Janssen Research & Development, LLC

Endocrinologic and Metabolic Drugs Advisory Committee

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Canagliflozin as an Adjunctive Treatment to Diet and Exercise Alone or Co-administered with Other Antihyperglycemic Agents to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus

JNJ-28431754 (Canagliflozin)
NDA 204042

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

4MSU	4-Month Safety Update
ACE	angiotensin-converting-enzyme
ACR	albumin-creatinine ratio
ADR	adverse drug reaction
AHA	antihyperglycemic agents
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Apo B	apolipoprotein B
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
AUC	area under the curve
beta-CTx	beta collagen type 1 carboxy-telopeptide
bid	twice daily
BMD	bone mineral density
BMI	body mass index
BOCF	baseline observation carried forward
BP	blood pressure
BUN	blood urea nitrogen
C_{max}	maximum concentration
CANA	canagliflozin
CEC	Clinical Events Committee
CFU	colony-forming unit
CI	confidence interval
CRF	case report form
CT	computed tomography
CV	cardiovascular
CVEAC	Cardiovascular Endpoint Adjudication Committee
DBP	diastolic blood pressure
dL	deciliter
DPP-4	dipeptidyl peptidase-4
DXA	dual energy X-ray absorptiometry
EAC	Endpoint Adjudication Committees
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ESRD	end stage renal disease
eGFR	estimated glomerular filtration rate
FAC	Fracture Adjudication Committee
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FS-MMTT	frequently-sampled mixed meal tolerance test
GFR	glomerular filtration rate
eGFR	estimated glomerular filtration rate
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated hemoglobin (hemoglobin A_{1c})
HDL-C	high-density lipoprotein-cholesterol
HEAC	Hepatic Events Assessment Committee
HOMA	homeostatic model assessment 2
HR	hazard ratio
IC_{50}	50% inhibition concentration
IDMC	Independent Data Monitoring Committee
ISE	Integrated Summary of Efficacy
ISR	insulin secretion rate
ISS	Integrated Summary of Safety
KIM-1	kidney injury marker-1
LCTs	Leydig cell tumors

LDL-C	low-density lipoprotein-cholesterol
LH	luteinizing hormone
LOCF	last observation carried forward
LS	least squares
MACE-plus	major adverse cardiovascular events plus events of hospitalized unstable angina
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMTT	mixed-meal tolerance tests
MRHD	maximal recommended human dose
MRP2	multidrug resistance protein 2
MTCP	Mitsubishi Tanabe Pharma Corporation
N	number of subjects
n	number of subjects in subset
NAG	N-acetyl-beta-D-glucosaminidase
ng	nanogram
OSOM	outer stripe of the outer medulla
P1NP	propeptide amino terminal of type I procollagen
PD	pharmacodynamic
PDLC	pre-defined limits of change
P-gp	P-glycoprotein
PK	pharmacokinetics
PPARγ	peroxisome proliferator-activated receptor agonists
PPG	post-prandial glucose
PTH	parathyroid hormone
qd	once-daily
RT_G	renal threshold for glucose
RTTs	renal tubular cell tumors
SAPs	statistical analysis plans
SBP	systolic blood pressure
SGLT1	sodium-glucose co-transporter 1
SGLT2	sodium-glucose co-transporter 2
SOC	System organ class
SU	sulphonylurea
$t_{1/2}$	elimination half-life
T2DM	type 2 diabetes mellitus
TG	triglycerides
T_{max}	time to maximal concentration
UGE	urinary glucose excretion
UGE_{24}	24-hour urinary glucose excretion
UGT	UDP-glucuronosyltransferase
µM	micromolar
UTI	urinary tract infection
WHO	World Health Organization

EXECUTIVE SUMMARY

The subject of this briefing book is a New Drug Application (NDA 204042) that was submitted by Janssen Research & Development, LLC (hereafter referred to as the sponsor) on behalf of Janssen Pharmaceuticals, Inc on 30 May 2012 for the use of canagliflozin 100 mg and 300 mg once-daily (qd) as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM).

Canagliflozin is an orally-active inhibitor of sodium-glucose co-transporter 2 (SGLT2). The SGLT2 protein, expressed in the renal proximal tubules, is responsible for the majority of the reabsorption of glucose filtered through the glomerulus; expression of SGLT2 is limited to the kidney. Filtered glucose is nearly fully reabsorbed until the transporters reach maximum reabsorptive capacity, the so-called transport maximum for glucose; the plasma glucose concentration at which this occurs is referred to as the renal threshold for glucose (RT_G). Above this threshold, urinary excretion of glucose increases in proportion to the plasma glucose concentration. By inhibiting SGLT2, canagliflozin lowers RT_G, resulting in increased excretion of glucose by the kidney; the increased urinary glucose excretion (UGE) directly lowers plasma glucose concentrations in patients with elevated glucose levels. In addition, the increased glucose excretion also results in a loss of calories, leading to weight loss. Although canagliflozin markedly lowers RT_G, the new RT_G setpoint is above the usual threshold for hypoglycemia (usually considered to be 70 mg/dL), so that the risk of hypoglycemia with this agent is low. In addition, the diuretic effect, related to the osmotic diuresis from increased UGE, likely contributes to reductions in blood pressure (BP)—potentially useful in patients with T2DM who have a high incidence of hypertension. Finally, inhibition of SGLT2 with increased UGE is a mechanism distinct from other current classes of antihyperglycemic agents (AHAs), not requiring the action of insulin for efficacy, with the potential for value in combination with a wide range of other agents in the treatment of patients with T2DM. Thus, canagliflozin provides an insulin-independent approach for control of hyperglycemia, useful across the continuum of the disease, providing glycemic efficacy in combination with the wide-range of other glucose-lowering agents, with a low risk for inducing hypoglycemia, and can also promote weight loss, and reduce BP.

The canagliflozin clinical program was designed to assess the safety and efficacy of canagliflozin in patients with T2DM. This program, the largest diabetes development program filed to date, consists of 52 completed or ongoing clinical studies, including data from 10,285 subjects (who received at least 1 dose of double-blind study drug) in 9 Phase 3 studies, 1,210 subjects in 3 Phase 2 studies, and 1,300 subjects in 40 Phase 1 studies.

A broad range of doses, from 50 mg to 1600 mg daily, was evaluated in Phase 1 studies with doses of up to 600 mg per day evaluated in Phase 2 trials. The results showed that canagliflozin at a dose of 100 mg provides substantial, and at a dose 300 mg provides maximal, sustained 24-hour reductions in RT_G, with 100 mg qd providing effective and 300 mg qd providing maximal lowering of fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA_{1c}).

In the Phase 3 studies, canagliflozin has been assessed as monotherapy, as add-on therapy with metformin, sulphonylurea (SU), metformin and SU, metformin and a peroxisome proliferator-activated receptor (PPARγ) agonist (pioglitazone), and as add-on therapy with insulin (with or without other AHAs). The Phase 3 program also includes studies in special populations of patients with T2DM: subjects with renal impairment (eGFR ≥30 to <50 mL/min/1.73 m^2); subjects with or at high risk for cardiovascular (CV) complications; and older subjects.

Glycemic Efficacy

The primary efficacy endpoint in each of the Phase 3 studies was the change from baseline in HbA_{1c}. The key secondary efficacy assessments included supportive glycemic endpoints (changes from baseline in FPG and 2-hour post-prandial glucose [PPG], and proportion achieving an HbA_{1c} target of <7.0%), along with endpoints associated with diabetic comorbidities, such as changes from baseline in body weight, systolic blood pressure (SBP), and lipid parameters of high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG).

Results of the Phase 3 studies demonstrated the efficacy of canagliflozin in reducing HbA_{1c} in a broad range of subjects with T2DM, both with recent onset as well as long-standing diabetes and on a range of different background AHAs. A clinically meaningful improvement in glycemic control was seen when canagliflozin was given as monotherapy and when given in dual combinations (add-on to metformin or to SU agents), in triple oral AHA combinations (add-on to metformin plus an SU agent or metformin plus pioglitazone), in combination with insulin (alone or in combination with other agents), or as an add-on to existing diabetes therapy (any approved oral or parenteral therapy). In the monotherapy study, HbA_{1c} reductions of -0.91% and -1.16% relative to placebo for canagliflozin 100 mg and 300 mg, respectively, were observed. In the studies examining specific add-on combination uses, the efficacy of canagliflozin in lowering HbA_{1c}, relative to placebo, was generally consistent ranging from -0.62% to -0.74% with the 100 mg dose and from -0.73% to -0.92% with the 300 mg dose. Across all studies, the 300 mg dose consistently provided greater HbA_{1c} lowering relative to the 100 mg dose; since reduction in diabetic microvascular complications is continuous with improvements in glycemic control, the additional glucose-lowering efficacy with the 300 mg dose is clinically relevant (UKPDS 2000, DCCT 1993).

Results of subgroup analyses performed in a pooled population of the placebo-controlled Phase 3 studies found no important differences when comparing the effect of canagliflozin in change from baseline in HbA_{1c} based on baseline demographic characteristics (age, sex, race, ethnicity), baseline body mass index (BMI), or geographic region. Greater reductions in HbA_{1c} relative to placebo were observed with canagliflozin among subjects with higher baseline HbA_{1c} and higher estimated glomerular filtration rate (eGFR) values compared with subjects with lower baseline values.

It was anticipated that the efficacy of canagliflozin would be dependent upon renal function, since the extent of UGE, above the RT_G, varies directly with eGFR (as well as plasma glucose concentrations). A dedicated Phase 3 study (DIA3004) in subjects with baseline eGFR values of

≥30 to <50 mL/min/1.73 m^2 confirmed that glycemic efficacy was still observed in subjects with these lower eGFR values, even though the reductions in HbA_{1c} and FPG were smaller than seen in subjects with higher baseline eGFR values. The observations from this dedicated study were confirmed and extended with a pooled population analysis of subjects drawn from 4 Phase 3 studies with baseline eGFR ≥30 to <60 mL/min/1.73 m^2 (Stage 3 disease based upon National Kidney Foundation [NKF] Classification). Both in the dedicated study in subjects with baseline eGFR values of ≥30 to <50 mL/min/1.73 m^2 and in the pooled analysis from 4 Phase 3 studies with subjects who had baseline eGFR values of ≥30 to <60 mL/min/1.73 m^2, a higher proportion of subjects attained glycemic goal (HbA_{1c} <7%) suggesting that canagliflozin can provide clinically useful efficacy in subjects with reduced renal function. Since the currently available antihyperglycemic agents used to treat patients with T2DM who have renal impairment have associated safety and tolerability limitations that are particularly of concern in this population (eg, insulin and SU with weight gain and hypoglycemia; PPARγ agonists with weight gain, fractures, and fluid retention), the availability of a new treatment option such as canagliflozin which is not associated with weight gain or hypoglycemia will give health care providers an additional means of improving glycemic control in this difficult to treat population.

Other Potentially Beneficial Effects

In addition to the observed glycemic improvements, treatment with canagliflozin resulted in consistent, statistically significant reductions in total body weight relative to placebo. This is particularly notable given the high prevalence of obesity in patients with T2DM, the contribution of excess body weight to the pathogenesis of the disease, and the weight gain associated with other classes of AHAs such as SU, insulin and PPARγ agonists. Weight loss with canagliflozin appeared dose-related (with -1.4% to -2.7% reductions with 100 mg and -1.8% to -3.7% reductions with 300 mg, relative to placebo), and was generally consistent across placebo-controlled Phase 3 studies. Results of specialized body composition investigations using dual energy X-ray absorptiometry (DXA) in 2 of the Phase 3 studies showed that the body weight reduction with canagliflozin was attributable to a greater decrease in body fat mass relative to lean body mass. The proportionate fat and lean body mass reductions observed with canagliflozin are similar to those previously reported with the other agents providing weight loss such as liraglutide or with reduced caloric diet-induced weight loss.

As previously noted, patients with T2DM commonly have hypertension, contributing to the increased risk that these patients have for both CV and microvascular complications. Reductions in SBP at the primary assessment time point were observed with canagliflozin in Phase 3 studies (ranging from -2.2 to -5.7 mm Hg of SBP with canagliflozin 100 mg dose, and -1.6 to -7.9 mm Hg with the 300 mg dose, relative to placebo, in placebo-controlled 26 week studies), and were generally statistically significantly greater for both doses relative to placebo, and also greater relative to comparator agents (glimepiride and sitagliptin).

Increases in HDL-C were observed with canagliflozin 100 mg and 300 mg in all Phase 3 studies, and were generally statistically significantly greater than those observed with placebo. While larger reductions in fasting TG with canagliflozin doses compared with placebo were seen in

most of the Phase 3 studies, the treatment difference was small and not usually statistically significant for individual studies.

Safety

The safety and tolerability profile that emerges from the development program for canagliflozin shows a medication that is overall well tolerated. The incidence of discontinuations due to adverse events was slightly higher than seen in the control group, though generally low. The small increase in discontinuations due to adverse events were generally related to specific adverse drug reactions (ADRs), described below, with each particular ADR infrequently leading to discontinuations; there was no increase in serious adverse events or deaths in the canagliflozin treatment groups relative to control groups.

Adverse drug reactions associated with canagliflozin include genital mycotic infections, urinary tract infections (UTIs), adverse events related directly to the osmotic diuresis (such as urinary frequency or thirst), and adverse events related to reduced intravascular volume (such as postural dizziness), as well as constipation, and a low incidence of rash or urticaria. In men, the genital mycotic infections (including balanitis and balanoposthitis) occurred predominantly in uncircumcised individuals, generally did not lead to discontinuation from the study. In women, genital mycotic infections (including candidal vulvovaginitis) also did not generally lead to discontinuation. A modest increase in the incidence of adverse events of UTI was observed with canagliflozin relative to control, without an increase in serious adverse events of UTI.

Adverse drug reactions were observed that relate to the osmotic diuretic effect of canagliflozin, with increases in UGE leading to a diuretic action; this included ADRs of pollakiuria (increased urinary frequency), polyuria (increased urinary volume), and thirst. Adverse drug reactions related to reduced intravascular volume were observed including postural dizziness, orthostatic hypotension, and hypotension. These adverse events were generally considered as mild or moderate in intensity, and infrequently led to discontinuation. No increase in serious adverse events related to reduced intravascular volume were seen with canagliflozin treatment. The reduction in intravascular volume also led to small, reversible mean reductions in eGFR.

Based on the observations from the 2-year rat carcinogenicity study (findings of renal tubular cell cancers, Leydig cell tumors [LCTs], and pheochromocytomas), an extensive preclinical toxicology program was conducted that demonstrated that these tumors related to effects of canagliflozin in rats, not seen in humans (including rises in luteinizing hormone [LH] associated with LCT, and carbohydrate malabsorption leading to associated metabolic effects, including marked hypercalciuria, inducing renal tubular tumors and pheochromocytomas). In the clinical program, there were no reports of LCT or pheochromocytoma and no imbalance in the low incidence across groups of renal cell cancers. Due to the reported imbalance in breast and bladder cancers for dapagliflozin, another SGLT2 inhibitor, the incidence of breast and bladder cancers were examined in the canagliflozin development program, with no imbalance in events observed.

In preclinical studies in rats, hyperostosis (increased trabecular bone) was observed; mechanistic toxicology studies demonstrated that hyperostosis, like the tumors discussed above, related to carbohydrate malabsorption in rats treated with canagliflozin, with consequent marked hypercalciuria (which is not seen in human). A detailed analysis of bone safety was conducted in the Phase 3 program, including an assessment using dual-energy X-ray absorptiometry (DXA) in a dedicated Phase 3 study (a study conducted in older subjects [ages ≥55 and ≤80 years] with T2DM) and a cross-program assessment of fracture incidence. The results of the DXA assessment at Week 52 showed small decreases in bone density at the lumbar spine and total hip, with slight trends towards increases seen at the femoral neck and distal forearm. The small reductions in bone density seen at the lumbar spine and total hip are likely related to the weight loss seen with canagliflozin (weight loss is known to be associated with reductions in bone mineral density [BMD]). A higher incidence of adjudicated fractures was observed with canagliflozin that was small and not statistically significant.

As noted above, increases in HDL-C and reductions in TG were observed with canagliflozin treatment; increases in low-density lipoprotein-cholesterol (LDL-C) were also observed: in a pooled analysis of placebo-controlled 26-week studies, increases in LDL-C relative to placebo of 4.4 mg/dL and 8.2 mg/dL at the 100 mg and 300 mg doses, respectively. The increases in LDL-C were associated with smaller increases in non-HDL-C and in apolipoprotein (Apo) B, and LDL particle number. The changes in the CV risk profile with canagliflozin include reductions in SBP and increases in LDL-C, both established CV risk factors, and validated as surrogate endpoints. Increases in Apo B, non-HDL-C, and LDL particle number were approximately half as large as the rise in LDL-C. Improvements in other endpoints associated with CV risk, but not established as surrogate endpoints for CV benefit, such as body weight, glycemic control, HDL-C, and TG were observed. The initial cross-program CV meta-analysis (including results from the dedicated CV safety study) observed an HR of 0.91 for a pre-specified composite endpoint of CV death, non-fatal MI, non-fatal, and hospitalized unstable angina (95% CI: 0.68, 1.22), showing no signal for an increase in the CV risk.

In summary, canagliflozin provided dose-related and substantial improvements in glycemic control, also providing other potential benefits including weight loss (predominantly fat mass), and reductions in blood pressure. Canagliflozin was overall well tolerated, with ADRs identified including genital mycotic infections, a small increase in UTIs, polyuria/pollakiuria and thirst, adverse events related to reduced intravascular volume (eg, postural dizziness), and a dose-related increase in LDL-C.

Based on its efficacy profile, canagliflozin has the potential to be a useful addition to currently available AHAs.

1. BACKGROUND

This document presents data from preclinical and clinical studies in support of the efficacy and safety of once-daily (qd), orally-administered canagliflozin as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM).

1.1. Development Rationale

Diabetes mellitus is a chronic disease that is growing in prevalence worldwide, with the vast majority of those afflicted having T2DM. In 2010, the worldwide prevalence of diabetes was estimated to be 285 million, with almost 90% of diabetic patients having T2DM (Hu 2011). This number is expected to grow to 366 million in 2030 (Wild 2004).

Type 2 diabetes mellitus is characterized by several key pathogenic defects that include decreased secretion of insulin by the pancreas and resistance to the action of insulin in various tissues (muscle, liver, and adipose); together these defects lead to reduced glucose uptake and endogenous glucose overproduction. Chronic hyperglycemia, in turn, contributes to further progressive impairment of insulin secretion and to worsening insulin resistance (so-called glucose toxicity) (Leahy 1992, Rossetti 1990), which further worsens control of blood glucose levels (Robertson 2006) and leads to the development of microvascular diabetic complications, including retinopathy, nephropathy, and neuropathy (Fowler 2008) and is a risk factor for heart disease (Klein 1995, Gaede 2003).

Various classes of antihyperglycemic agents (AHAs) are now available with different pharmacologic targets. Biguanides (metformin) target hepatic insulin resistance by decreasing the amount of glucose made by the liver while increasing glucose uptake in skeletal muscle. Sulphonylureas and other insulin secretagogues increase beta-cell insulin secretion. Insulin sensitizers (eg, thiazolidinediones) target adipocytes and muscle to decrease insulin resistance and increase cellular utilization of glucose. Glucagon-like peptide-1 (GLP-1) and dipeptidyl peptidase-4 (DPP-4) inhibitors both target enhancing the incretin hormone axis, leading to increased insulin secretion and lower glucagon levels. Alpha-glucosidase inhibitors, such as acarbose, delay intestinal carbohydrate absorption.

Despite the availability of a range of therapeutic options, only approximately half of patients with T2DM are at target glycemic control, even with administration of combinations of the currently available medications (Lawrence 2006). Many of the current T2DM treatments are associated with safety or tolerability issues, including hypoglycemia, edema, or gastrointestinal adverse experiences which can limit dose and hence therapeutic benefit. Further, some of the current AHAs are associated with weight gain, which is particularly problematic as many patients with T2DM are overweight or obese. Additional weight gain can increase insulin resistance, an underlying pathophysiologic mechanism of T2DM, and also reduce adherence to medication (Russell-Jones 2007). Most patients with T2DM are initially managed with single-agent therapy, usually metformin (Bennett 2012). Over time, patients often require more intensive regimens, with combinations of 2 or 3 agents, and eventually require subcutaneously administered therapies, such as insulin to maintain target glycemic control—still with many patients not at glycemic goals. Underlying the need for the increasingly complex treatment regimens is a progressive loss of beta-cell mass and function, with consequent diminished insulin secretion. Improved glycemic control has been demonstrated to reduce the occurrence of diabetic microvascular complications—as a continuous relationship (UKPDS 2000, DCCT 1993); hence, getting to recommended HbA_{1c} targets is an important goal for physicians managing patients with diabetes. There are several reasons that patients do not get to glycemic goals—with the

limitations of current AHAs an important one. There remains a substantial unmet medical need for new medications to treat patients with T2DM that are safe and efficacious, beneficially impact beta-cell function and insulin secretion, provide good durability, do not lead to weight gain—or even provide weight loss—and have a low risk of hypoglycemia.

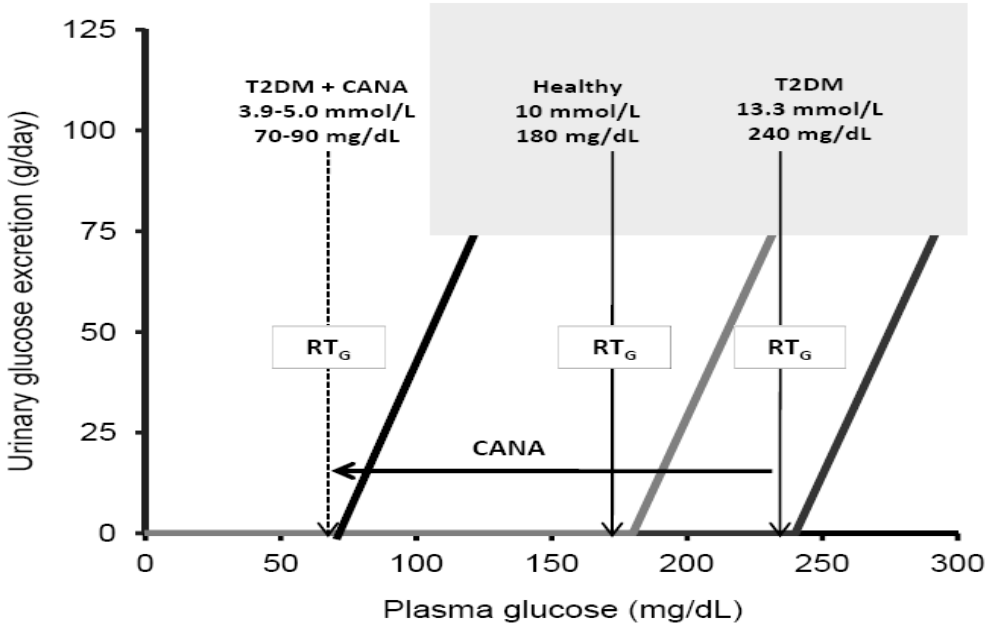
Canagliflozin is an orally-active inhibitor of sodium-glucose co-transporter 2 (SGLT2) that has been studied in an extensive Phase 3 clinical development program involving approximately 10,300 subjects with T2DM (1,088 of whom had renal impairment [eGFR 30 to <60 mL/min/1.73 m^2]). This document provides an overview of the mechanism of action, pharmacology, and efficacy and safety of canagliflozin.

1.2. Mechanism of Action

In healthy individuals, glucose is freely filtered through the renal glomerulus and then reabsorbed in the proximal tubules. Glucose reabsorption in the renal tubules is largely due to 2 key glucose transporters: SGLT2 and sodium-glucose co-transporter 1 (SGLT1). The SGLT2 is a high-capacity and low-affinity glucose transporter expressed in the proximal renal tubules, and not in other tissues, that is responsible for the majority of the reabsorption into the blood stream of glucose filtered through the glomerulus (Bakris 2009, Vaidya 2010). Sodium-glucose co-transporter 1 is highly expressed in the intestine and is largely responsible for intestinal glucose and galactose absorption (Wright 2001). Nearly all glucose filtered through the glomerulus is re-absorbed until the transporters reach maximum reabsorptive capacity; the glucose concentration at which this occurs is referred to as renal threshold for glucose (RT_G). Above this threshold, urinary excretion of glucose increases in proportion to the plasma glucose concentration. Since the load of filtered glucose is proportional to the glomerular filtration rate (GFR), urinary glucose excretion (UGE) above the RT_G also varies with GFR. In patients with T2DM, the RT_G is elevated (Figure 1), leading to increased glucose reabsorption despite hyperglycemia which likely contributes to sustained elevation in serum glucose concentrations (DeFronzo 2009).

Canagliflozin is a competitive, reversible inhibitor of SGLT2 that lowers the RT_G, thus reducing reabsorption of filtered glucose, increasing UGE (Figure 1), and thereby lowering plasma glucose concentrations in patients with T2DM; this mechanism is independent of insulin secretion, so would be expected to be effective across the spectrum of beta cell function, from new onset patients with moderate impairment of beta-cell function to patients with greater beta-cell functional loss such as those with long-standing diabetes who require insulin.

Figure 1: Inhibition of SGLT2 by Canagliflozin Leads to Increased Renal Glucose Excretion and Improved Glucose Homeostasis



Besides lowering plasma glucose concentrations, the increased UGE with SGLT2 inhibition also translates to an osmotic diuresis, with the diuretic effect likely contributing to a reduction in systolic blood pressure (SBP). In addition, a loss of caloric equivalents (4 kcalories/gram of glucose) translates to a reduction in body weight.

Although canagliflozin is a potent inhibitor of SGLT2, it is also a lower potency inhibitor of SGLT1 (difference in potency is approximately 160:1). In Phase 1 studies, reduced glucose excursion after a meal was observed in healthy volunteers with pre-meal administration of higher doses of canagliflozin, an effect that did not appear to relate to greater UGE (with doses ≥100 mg providing effective inhibition of SGLT2 and doses of >200 mg providing greater reductions in meal glucose excursion). Subsequent clinical studies have confirmed a reduced rate of intestinal glucose absorption; it is hypothesized that after tablet dissolution, transiently high gut drug concentrations of canagliflozin may inhibit luminal SGLT1, leading to delayed glucose absorption. Several mechanistic studies in humans have shown that, despite delayed glucose absorption, glucose malabsorption is not induced. Although intestinal SGLT1 inhibition, related to high luminal concentrations, may be observed, even at peak (maximum concentration [C_{max}]) plasma concentrations, no substantive inhibition of SGLT1 systemically would be expected.

1.3. Proposed Indication and Posology

The proposed indication for canagliflozin is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The proposed recommended dose of canagliflozin is 100 mg or 300 mg qd, preferably taken before the first meal of the day. Based on a dose-related increase in incidence of adverse events related to reduced intravascular volume in patients on a loop diuretic, or those with moderate renal impairment, or those ≥75 years of age, a starting dose of 100 mg qd should be considered for patients with one or more of these characteristics.

2. TOXICOLOGY

In repeat-dose studies in mice, rats and dogs, canagliflozin elicited a number of effects that were associated with SGLT2 inhibition, such as increased urine volume due to high concentrations of urinary glucose compared with controls. In addition to being a potent SGLT2 inhibitor, canagliflozin also possesses intrinsic, albeit less potent, SGLT1 inhibitory activity: 50% inhibition concentration (IC_{50}) for rat SGLT2 and SGLT1 are 3.7 and 571 nmol/L, respectively. Expressed on the luminal surface of enterocytes, SGLT1 is responsible for the intestinal absorption of glucose and galactose. During dissolution prior to drug absorption in the intestinal lumen, canagliflozin can reach concentrations high enough to inhibit intestinal luminal SGLT1 glucose transport.

Following administration of high oral doses in rat toxicity studies, canagliflozin causes glucose/galactose malabsorption as demonstrated by the increased content of glucose and reduced pH in the distal gastrointestinal tract – findings consistent with carbohydrate malabsorption. Inhibition of carbohydrate absorption was confirmed by the ability of canagliflozin treatment in rats to block the absorption of an orally administered, non-metabolizable sugar transported by SGLT1 (3-O-methyl glucose). In humans treated with canagliflozin at the same or higher doses than studied in the Phase 3 program, canagliflozin was not associated with glucose malabsorption as assessed by absorption of radiolabeled glucose or by hydrogen breath content following an oral glucose challenge, a test used to diagnose glucose malabsorption. Thus, carbohydrate malabsorption is present in rats, but not in humans, treated with canagliflozin.

By inducing carbohydrate malabsorption, leading to reduced pH in the distal gastrointestinal tract of rats, oral canagliflozin administration leads to increases calcium solubility and enhances non-vitamin D-dependent calcium absorption as demonstrated by increased intestinal absorption of radio-labeled calcium in rats orally administered canagliflozin. The increased calcium absorption in canagliflozin treated rats was associated with marked increases (>10-fold) in urinary calcium excretion (Attachment 1, Table 1). In response to the increased intestinal calcium absorption, marked decreases in parathyroid hormone (PTH), 1,25-dihydroxyvitamin D and markers of bone turnover were seen in rats treated with canagliflozin (Attachment 1Table 1). Increases in trabecular bone content (hyperostosis) were also seen in rats, but not dogs or mice, treated with canagliflozin (Attachment 1, Table 1).

Unlike glucose and galactose whose intestinal absorption is mediated by SGLT1, the intestinal absorption of fructose is mediated by GLUT5, a monosaccharide transporter not inhibited by canagliflozin (Drozdowski 2006). Studies in rats substituting fructose for glucose and galactose in the diet, to avoid carbohydrate malabsorption, prevented canagliflozin-induced increases in urinary calcium excretion, decreases in PTH, 1,25-dihydroxyvitamin D and markers of bone turnover and hyperostosis (Attachment 1, Table 1). Hypercalciuria and hyperostosis in rats treated with canagliflozin are also observed with selective SGLT1 inhibitors (Kissner 2010), and with high doses of other SGLT2 inhibitors including dapagliflozin (Tirmenstein 2010). Since carbohydrate malabsorption and alterations in the calcium axis are not seen in humans treated

with canagliflozin (Section 6.5.2), the hyperostosis in rats is not considered to be of clinical relevance.

Canagliflozin was negative in standard genotoxicity testing. A 2-year carcinogenicity study in mice showed no treatment related increase in tumors at systemic exposures similar to those observed in the 2-year rat carcinogenicity study. In a 2-year rat carcinogenicity study, an increase in 3 tumor types was seen in rats treated with canagliflozin (Attachment 1 Table 2): Leydig cell tumors (LCTs) of the testes, renal tubular cell tumors (RTTs), and pheochromocytomas (adrenal medullary tumors). Leydig cell tumors were observed at all dose levels so that a no observable effect level could not be determined. Renal tubular tumors and pheochromocytomas were observed only at the high dose (100 mg/kg/d) and the no observable effect level was the mid dose of 30 mg/kg/d (17x and 4.5x the maximal recommended human dose [MRHD] of 100 mg and 300 mg, respectively). For all 3 tumors types, there is strong evidence that the mechanisms for induction of the tumors are specific to the rat, as described below.

Spontaneous and drug-induced LCTs are commonly observed in male rats (Clegg 1997; Prentice 1995). A wide range of medications have been associated with LCTs in rats, but have not been reported to cause LCTs in humans (Cohen 2011; Cook 1999; Precose® 2011). An increase in luteinizing hormone (LH), a Leydig cell mitogen, is an established mechanism shared by a number of non-genotoxic agents causing LCTs in rats (Clegg 1997). In a 6-month study, canagliflozin treatment under conditions causing LCTs induced statistically significant increases in LH (1.5- to 1.8-fold), relative to vehicle-treated animals; this is the range seen with other non-genotoxic agents causing LCT in rats by an LH-dependent mechanism (Cook 1999). In clinical studies, in male subjects treated for 12 weeks, canagliflozin 300 mg qd did not increase LH levels. Based on the evidence for an established LH-mediated mechanism in rats and the lack of an effect of canagliflozin on LH levels in humans, canagliflozin-induced LCT in rats are not considered to be relevant to human safety.

Acarbose induces carbohydrate malabsorption, and in rats (but not in hamsters), is associated with an increased occurrence of RTTs and LCTs (Precose® Prescription Information Precose 2011). Acarbose, used clinically for over 20 years, has not been associated with an increase in the incidence of these tumors in humans (Roe 1989, Hollander 1992). In rats, poorly absorbable sugars (eg, lactose) cause pheochromocytomas (Greim 2009). Carbohydrate malabsorption has been postulated as being a critical to the pathogenesis of RTT and pheochromocytomas in rats (Bär 1992, Hollander 1992, Precose 2011). To assess whether carbohydrate malabsorption was involved in canagliflozin-induced pheochromocytoma and RTT formation, adrenal medullary and renal tubule cell proliferation, a critical step in tumorigenesis, was examined. After 1-, 3-, and 6 months in rats fed a glucose/galactose diet treated with canagliflozin at doses previously demonstrated to cause tumor formation, adrenal medullary and renal tubule cell proliferation were increased, relative to vehicle treated animals (Attachment 1, Table 3). Substituting fructose for glucose/galactose in the diet, thus avoiding carbohydrate malabsorption, prevented canagliflozin-induced increases in adrenal medullary and renal tubule cell proliferation (Attachment 1, Table 3). Tumors can occur due to increased cell proliferation secondary to cell injury (Lock 2004), therefore renal tubule

injury was examined microscopically, including evaluation of kidney injury marker-1 (KIM-1) expression which increases with renal tubule injury. In rats fed the glucose/galactose containing diet, canagliflozin treatment was associated with microscopic evidence of tubule injury (increased cytoplasmic vacuolation of renal tubular cell and an increase in exfoliated pyknotic cells in the tubular lumen of rats) and a marked increase in KIM-1 staining (Attachment 1, Table 4). Avoidance of carbohydrate malabsorption by feeding a glucose/galactose-free diet in canagliflozin treated rats prevented these signs of renal tubule injury. These data demonstrate that pheochromocytomas and RTTs in canagliflozin-treated rats are associated with carbohydrate malabsorption (related to intestinal SGLT1 inhibition) and not due to SGLT2 inhibition. The lack of malabsorption in humans treated with canagliflozin indicates that these tumors are not of clinical relevance.

Based on these nonclinical and clinical mechanistic studies showing that rat-specific mechanisms, not operative in humans, are responsible for LCTs, RTTs and pheochromocytomas seen in the rat carcinogenicity study, the sponsor concluded that the LCTs, RTTs, and pheochromocytomas are not relevant to human safety.

Canagliflozin was phototoxic in vitro in mouse fibroblasts exposed to UV-A light and in a single oral dose was phototoxic to the skin (≥50 mg/kg) of pigmented rats. Canagliflozin was not mutagenic in a photo-Ames test. Based on lack of photosensitivity in humans (see Section 6.11), the non-clinical phototoxicity findings are not considered to have clinical relevance.

3. CLINICAL PHARMACOLOGY

The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of canagliflozin were studied in 35 Phase 1 clinical pharmacology studies and in 5 biopharmaceutic studies. Clinical pharmacology studies were conducted in healthy subjects (n=721), subjects with T2DM (n=192) and in subjects with hepatic (n=16) or renal impairment (n=40). The PK and PD of canagliflozin were assessed following single oral doses of 10 to 1,600 mg, and multiple oral doses of 10 mg qd to 400 mg twice daily (bid).

3.1. Pharmacokinetics

3.1.1. Absorption and Distribution

The mean absolute oral bioavailability of canagliflozin was approximately 65% (90% confidence interval [CI]: 55.4%; 76.1%) for a single 300 mg dose. The absence of a food effect was demonstrated for the 300 mg tablet formulation. Thus, canagliflozin may be taken without regard to meals. However, based on the potential to reduce post-prandial glucose (PPG) excursions due to delayed intestinal glucose absorption at the 300 mg dose, it is recommended that canagliflozin preferably be taken before the first meal of the day, similar to how canagliflozin was administered in the Phase 3 studies.

The PK of canagliflozin is similar in healthy and T2DM subjects. After single-dose oral administration of 100 mg and 300 mg in healthy subjects, canagliflozin was rapidly absorbed, with median time to maximal concentration (T_{max}) occurring 1 to 2 hours postdose. Across the

range of 25 to 1,600 mg single doses in healthy subjects, mean canagliflozin AUC_{∞} increased in an approximately dose-proportional manner, whereas mean C_{max} increased in an approximately dose-proportional manner up to 1,200 mg, but was similar at the highest 2 doses studied (1,200 and 1,600 mg). Table 1 shows PK values following single and multiple dose administration of canagliflozin for 100 mg and 300 mg doses.

Table 1: Pharmacokinetic Parameters of Canagliflozin Following Single-Dose and Multiple-Dose Administration of 100 and 300 mg Canagliflozin in Healthy Subjects (Pooled Analysis)

	100 mg			300 mg		
Parameter	N	Mean (SD)	%CV	N	Mean (SD)	%CV
			Single Dose			
t_{max}, h [a]	33	1.50 (1.00 - 5.00)	-	178	1.98 (0.98 - 6.00)	-
C_{max}, ng/mL	33	1,059 (274)	25.9	178	2,792 (760)	27.2
AUC_{∞}, ng.h/mL	28	6,818 (1,542)	22.6	176	22,953 (5,633)	24.5
			Multiple Dose			
t_{max}, h [a]	38	1.00 (1.00 - 4.00)	-	114	1.42 (1.00 - 6.00)	-
C_{max}, ng/mL	38	1,029 (221)	21.5	114	3,148 (866)	27.5
AUC_{24h}, ng.h/mL	38	6,247 (1,196)	19.1	114	22,612 (5,051)	22.3

CV = coefficient of variation
[a] Median (range)

Steady state was reached after 4 to 5 days of daily dosing with canagliflozin 100 and 300 mg. Canagliflozin has time-independent PK: plasma AUC of canagliflozin increased up to 36% between the single dose and the steady state at Day 7, following 100 mg and 300 mg doses at steady-state and was predictable based on its half-life.

The mean apparent volume of distribution for canagliflozin at steady state after intravenous administration was 119 L, and the mean apparent volume of distribution based on the terminal elimination phase following single- and multiple-dose administration ranged between 221 and 402 L. These values exceed the volume of total body water (42 L).

Canagliflozin binds to both albumin and α-acid glycoprotein in the plasma with a total binding of ~98.3% to 99.2%, across a broad range of plasma concentrations (200 to 20,000 nanogram [ng]/mL) which encompasses higher than the therapeutic concentration range for canagliflozin in T2DM patients in and special populations.

3.1.2. Metabolism and Excretion

O-glucuronidation is the major metabolic elimination pathway for canagliflozin in humans. The major human plasma metabolites of canagliflozin are the ether (*O*)-glucuronides M5 formed by UDP-glucuronosyl transferase [UGT]2B4) and M7 (formed by UGT1A9). Unchanged drug was the major plasma drug-related peak in humans accounting for approximately 57% of plasma AUC of total drug-related material. In human plasma, the two *O*-glucuronide conjugates of unchanged drug, M5 and M7, were present at concentrations up to approximately 30% of total drug-related materials in plasma up to 12 hours postdose, but plasma AUC values were similar (M7) or less (M5) than those for canagliflozin. Both of these metabolites (M5 and M7) are

highly water soluble, chemically non-reactive and pharmacologically inactive with respect to SGLT2 and SGLT1 inhibition in vitro, and fall under the category of metabolites of no toxicologic concern (US FDA Guidance for Industry 2008). Further, both of these metabolites (M5 and M7) were detected in preclinical species (mouse, rat, or dog) used in the safety/toxicology studies of canagliflozin and exposure to these metabolites were observed in rats at levels similar or higher than exposures in human subjects with the 100 mg and 300 mg qd doses used in the clinical program. A minor oxidative metabolite (M9), formed predominantly by CYP3A4, represented <4% of the total drug-related components in plasma.

Following oral administration of [^{14}C]-canagliflozin to healthy subjects, 60.4% of the administered radioactive dose was recovered in feces (55.2% in fecal extracts and the remaining 5.2% in fecal extract residues and lyophilized fecal samples). Based on metabolite profiling of fecal extracts in which 55.2% of the total radioactive dose was recovered, excretion in feces was mainly as canagliflozin (41.5%), metabolite M9 (7.0%), and metabolite M7 (3.2%). Approximately 32.5% (13.3% as metabolite M5 and 17.2% as metabolite M7) of the administered dose was excreted in urine. Less than 1% of the administered dose was recovered as unchanged drug in urine.

Mean terminal plasma elimination half-life of canagliflozin was 10.6 and 13.1 hours with canagliflozin doses of 100 and 300 mg, respectively, based on pooled data from healthy subjects. This supports once-daily dosing.

3.2. Influence of Intrinsic Factors on Canagliflozin Pharmacokinetics

3.2.1. Renal Impairment

Canagliflozin C_{max} was not meaningfully altered by renal impairment. Compared with subjects with normal renal function, canagliflozin AUC_{∞} was increased by approximately 15%, 29%, and 53% in subjects with mild (eGFR 60 to <90 mL/min/1.73 m^2), moderate (eGFR 30 to <60 mL/min/1.73 m^2), and severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2), respectively, but was similar for subjects with end stage renal disease (ESRD). Population PK analysis was used to predict steady-state canagliflozin 24-hour area under the curve (AUC_{24h}) values for a typical population of subjects with T2DM for the highest dose (300 mg qd) and the highest dose studied in long-term clinical studies (300 mg bid). The final population PK model predicted that the mean steady-state canagliflozin AUC_{24h} values for the 300 mg qd and 300 mg bid doses were 24,941 ng.h/mL (95% CI: 24,311 to 25,571 ng.h/mL) and 54,258 ng.h/mL (95% CI: 50,623 to 57,893 ng.h/mL), respectively. Thus, based on these predictions, increases in canagliflozin steady-state AUC_{24h} by up to 118% compared with that for a 300 mg qd canagliflozin dose would not be considered to pose any safety concerns. The absence of safety signals in the 12-week Phase 2 dose-ranging study DIA2001 in subjects with T2DM treated with 300 mg bid canagliflozin supports this assessment. Therefore increases in canagliflozin AUC of this magnitude observed in renally impaired subjects are not considered clinically relevant. Canagliflozin was negligibly removed by hemodialysis.

3.2.2. Hepatic Impairment

In subjects with mild and moderate hepatic impairment, mean plasma C_{max} and AUC of canagliflozin were up to 7% and 11% higher, respectively, compared with healthy matched controls (DIA1013). These differences are not considered to be clinically meaningful. The effect of severe hepatic impairment on canagliflozin exposure has not been studied, and therefore canagliflozin will not be recommended for use in this population.

3.2.3. Age, Sex, Weight, and Race

Population PK analysis of pooled data from Phase 1, Phase 2, and Phase 3 studies (n=1,616 subjects) indicated that the covariates of age, sex, diabetes, body weight, body mass index, genetic polymorphisms in the UGT1A9*3 allele, and race did not have any meaningful effects on the disposition of canagliflozin.

3.3. Potential for Drug-Drug Interactions

3.3.1. Potential for Canagliflozin to Affect Other Drugs

Canagliflozin did not induce expression of CYP1A2, 2B6, 2C9, 2C19, and 3A4 enzymes at a concentration of 15 micromolar (μM) (6,660 ng/mL) in cultured human hepatocytes. In human liver microsomes, canagliflozin did not inhibit CYP1A2, 2A6, 2C19, 2D6, and 2E1 enzymes (IC50 values of >100 μM, [>44,400 ng/mL]) and weakly inhibited CYP2B6 (16 μM [7,104 ng/mL]), CYP2C8 (75 μM [33,300 ng/mL]), CYP2C9 (80 μM [35,520 ng/mL]), and CYP3A4 (27 μM [11,988 ng/mL]).

Based on in vitro data and the clinical drug-drug interaction studies conducted to date, the potential for clinically significant CYP450-based PK interactions appears to be low at canagliflozin doses in the therapeutic range (Table 2). Canagliflozin had no clinically relevant effects on the PK of metformin, the individual components of an oral contraceptive (containing ethinyl estradiol and levonorgestrel, CYP3A4 substrates), simvastatin (substrate of CYP3A4 and OATP1B1), glyburide and warfarin (CYP2C9 substrates), digoxin (P-glycoprotein (P-gp) substrate), and hydrochlorothiazide. Therefore, meaningful interactions would not be expected for other CYP3A4, CYP2C9, and P-gp substrates. No clinically relevant drug-drug interactions with CYP2B6 substrates are expected based on Simcyp physiologically-based PK simulation results. Thus, for common medications that patients with T2DM might be treated with (statins such as simvastatin, or antihyperglycemic agents including metformin and sulphonylurea [SU] agents or diuretics such as hydrochlorothiazide) no interactions with canagliflozin were observed. Canagliflozin is highly protein bound (98.3% to 99.2%) and when coadministered with drugs that are highly protein bound to plasma proteins such as glyburide (98%), warfarin (99.5%), or simvastatin (95%) in the drug-drug interaction studies, no clinically relevant effects were observed on the PK of these drugs. Therefore a significant drug-drug interaction due to displacement of concomitantly administered medications from plasma proteins by canagliflozin is unlikely.

Table 2: Overview of Effect of Canagliflozin on the Exposure of Other Drugs – Geometric Mean Ratios of the C_{max} and AUC of Other Drugs Following Co-Administration Compared with Canagliflozin Administration Alone

Co-Administered Drug	Dose of the Co-Administered Drug [a]	Dose of Canagliflozin [a]	Geometric Mean Ratio, %		
			Drug	AUC [b]	C_{max}
Ethinyl Estradiol and Levonorgestrel	0.03/0.15 mg	200 mg qd for 6 days	Ethinyl estradiol Levonorgestrel	106.61 106.33	122.21 122.32
Glyburide	1.25 mg	200 mg qd for 6 days	Glyburide 3-cis-hydroxy-glyburide 4-trans-hydroxy-glyburide	102.25 101.04 102.52	92.89 98.97 95.74
Warfarin	30 mg	300 mg qd for 12 days	(R)-warfarin (S)-warfarin INR	100.62 106.14 100.33 [c]	102.96 100.98 105.25
Simvastatin	40 mg	300 mg qd for 6 days	Simvastatin Simvastatin acid HMG-CoA reductase inhibitory activity	112.11 118.26 102.11	109.09 126.10 94.45
Digoxin	Day 1: 0.5 mg, then 0.25 mg for 6 days	300 mg qd for 7 days	Digoxin	119.51	135.82
Metformin	1,000 mg 2,000 mg	100 mg qd for 5 days 300 mg qd for 5 days	Metformin Metformin	96.5 119.95	85.6 105.80
HCTZ	25 mg qd for 35 days 25 mg qd for 35 days	200 mg qd for 7 days 300 mg qd for 7 days	HCTZ HCTZ	100.95 99.46	109.09 93.93
Acetaminophen	960 mg 1,000 mg	300 mg 100 mg qd for 25 days 300 mg bid for 25 days	Acetaminophen Acetaminophen Acetaminophen	99.1 [d] 102.26 [e] 105.67 [e]	96.5 108.01 100.32

[a] Single dose, unless noted otherwise.
[b] AUC_{∞} for single-dose administration and AUC_{24h} for multiple-dose administration.
[c] AUC_{last}.
[d] $AUC_{0\text{-}6h}$.
[e] $AUC_{0\text{-}12h}$

3.3.2. Potential for Other Drugs to Affect Canagliflozin

Since canagliflozin is primarily metabolized by UGT1A9 and UGT2B4 to the *O*-glucuronides M7 and M5, respectively, and undergoes minimal oxidative metabolism (approximately 7%), co-administration of drugs that are specific CYP inhibitors or inducers is not likely to affect the PK of canagliflozin.

Drug interaction studies were performed in humans to evaluate the effects of drugs known to inhibit or induce pathways involved in canagliflozin metabolism and elimination (UGT1A9, UGT2B4, P-gp, and multidrug resistance protein 2 [MRP2]) (Table 3).

Rifampin, a nonselective inducer of several UGT enzymes (eg, UGT1A1, 1A4, 1A9, and 2B7) and drug transporters, P-gp, and MRP2, decreased the C_{max} and AUC_{∞} of canagliflozin by 28% and 51%, respectively. These decreases in exposure to canagliflozin may decrease efficacy. If a combined inducer of these UGTs and drug transport systems (eg, rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with canagliflozin, monitor glycosylated

hemoglobin (HbA_{1c}) in patients receiving canagliflozin 100 mg qd with consideration to increasing the dose to 300 mg qd if additional glycemic control is needed.

Probenecid, a nonselective inhibitor of several UGT enzymes and drug transporters including UGT1A9 and MRP2, had no clinically relevant effect on the PK of canagliflozin. Because canagliflozin undergoes glucuronidation by 2 different UGT enzymes and glucuronidation is a high-capacity/low-affinity system, clinically relevant interactions of other drugs on canagliflozin PK via inhibition of glucuronidation are unlikely to occur.

Cyclosporine, an inhibitor of P-gp, CYP3A, and several drug transporters including MRP2, had no clinically relevant effect on the PK of canagliflozin. No meaningful interactions with other P-gp inhibitors would be expected.

As canagliflozin is bound to both plasma proteins (albumin and α-acid glycoprotein) it is less likely to be affected by displacement binding interactions. Plasma protein binding of canagliflozin was unaffected in patients with renal and hepatic impairment. Further for drugs with low extraction ratio like canagliflozin, PK is not expected to be affected by displacement protein-binding interactions from other drugs. Changes in plasma protein binding have little clinical relevance.

Table 3: Overview of Effect of Other Drugs on Canagliflozin Exposure – Geometric Mean Ratios of the C_{max} and AUC of Canagliflozin Following Co-Administration Compared with Canagliflozin Administration Alone

Co-Administered Drug	Dose of the Co-Administered Drug [a]	Dose of Canagliflozin [a]	Geometric Mean Ratio, %	
			AUC [b]	C_{max}
Rifampin	600 mg qd for 9 days	300 mg	48.76	71.75
Probenecid	500 mg bid for 3 days	300 mg qd for 17 days	120.74	113.37
Cyclosporine	400 mg	300 mg qd for 8 days	122.98	100.81
Ethinyl Estradiol and Levonorgestrel	0.03/0.15 mg	200 mg qd for 6 days	91.39	91.57
Metformin	2,000 mg	300 mg qd for 5 days	109.76	105.17
HCTZ	25 mg qd for 35 days	200 mg qd for 7 days	109.07	106.77
	25 mg qd for 35 days	300 mg qd for 7 days	112.24	114.86

[a] Single dose, unless noted otherwise.
[b] AUC_{∞} for single-dose administration and AUC_{24h} for multiple-dose administration.

3.4. Pharmacodynamics

3.4.1. Responses to Inhibition of SGLT2 / Predicted SGLT1 Inhibition

In healthy subjects, mean 24-hour urinary glucose excretion (UGE_{24h}) increased in a dose dependent manner, with an apparent saturation of effect at doses of >200 mg qd providing UGE_{24h} values of approximately 60 to 70 g. In subjects with T2DM, UGE_{24h} was greater than in healthy subjects, generally 80 to 100 g at doses of ≥100 mg canagliflozin.

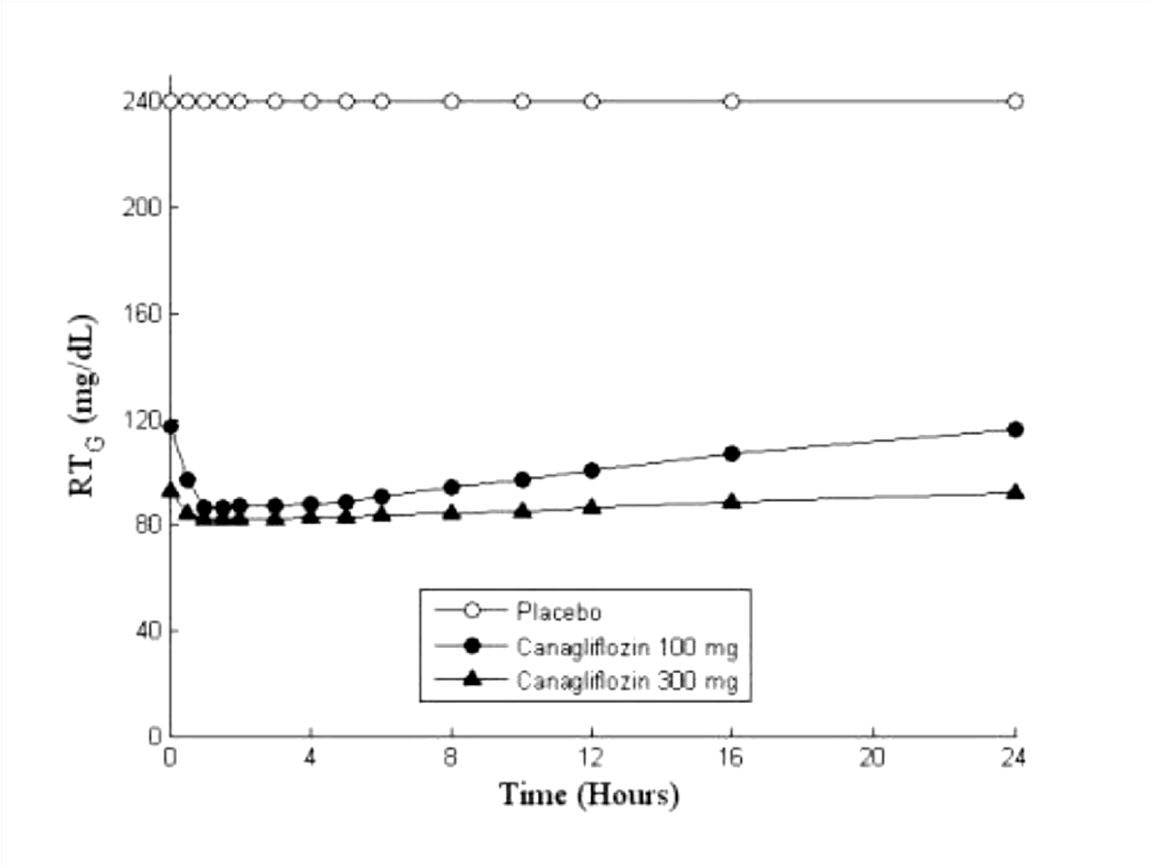
As described in Section 1.2, RT_G is the plasma concentration at which renal glucose resorptive capacity becomes saturated and above which glucose is excreted into the urine: when plasma glucose concentrations are above RT_G, the rate of UGE increases linearly with plasma glucose

concentrations, whereas only minimal UGE is observed when plasma glucose concentrations are below RT_G.

The sponsor developed and validated a new method to determine RT_G in clinical studies with canagliflozin (the method utilizes plasma and urinary glucose measurements after an oral glucose load and was validated by comparison of RT_G measured using this method with RT_G measured by the "gold standard" method of a stepped glycemic clamp). The mean baseline value of RT_G in the subjects studied with T2DM was approximately 240 mg/dL (13.3 mmol/L), which is higher than the commonly reported values of 180 to 200 mg/dL (10 to 11 mM) in non-diabetic, healthy subjects. Canagliflozin was shown to decrease 24-hour mean RT_G in a dose- and exposure-dependent manner, with maximal reduction to approximately 50 to 60 mg/dL (2.8 to 3.3 mmol/L) in healthy subjects and to approximately 70 to 90 mg/dL (3.9 to 5.0 mmol/L) in subjects with T2DM, suggesting a low risk for treatment-induced hypoglycemia.

Canagliflozin doses of ≥200 mg qd provided sustained near-maximal reductions in RT_G throughout the full 24-hour dosing interval, whereas the 100 mg dose provided near-maximal reductions in RT_G during the first 13 hours after dosing, followed by a modest rise in RT_G during the period of 13 to 24 hours after dosing, with fasting RT_G of approximately 110 mg/dL (see Figure 2). The decreases in RT_G observed on the first day of treatment were sustained throughout a 4-week double-blind treatment period in a study of subjects with T2DM. Similarly, in a 12-week study in subjects with T2DM, sustained increases in UGE were observed.

Figure 2: Predicted (PK/PD Modeled) 24-Hour Profile for RT_G in Subjects with Type 2 Diabetes Treated with Canagliflozin 100 mg and 300 mg



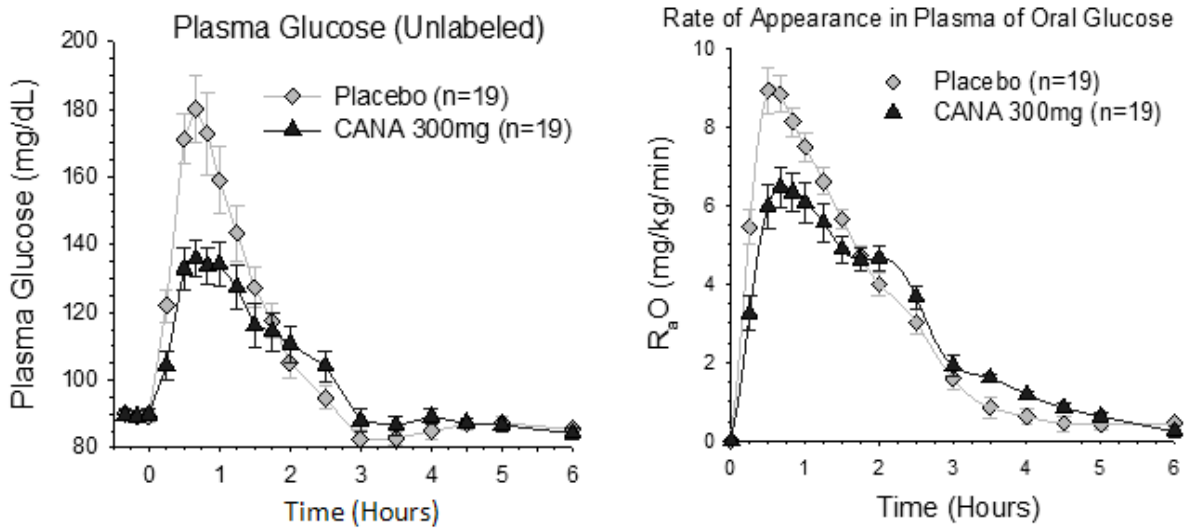
No biomarker is currently available for evaluating systemic SGLT1 inhibition in vivo, therefore the potential for SGLT1 inhibition with canagliflozin was assessed using the available preclinical and clinical data by comparing the measured plasma drug concentrations with in vitro estimates of IC_{50} for SGLT1 inhibition. It was assumed that the effective drug concentrations for systemic SGLT1 inhibition are equal to the free (non-protein-bound) drug concentrations in the plasma. This assumption appears consistent with measured effects of canagliflozin on SGLT2-mediated renal glucose uptake. The free drug concentrations remained well below the IC_{50} for SGLT1 inhibition even at C_{max} concentrations (IC_{50}: 663 nM vs mean C_{max} of unbound canagliflozin of 105 to 179 nM at the 300 mg dose in study DIA1023 [assuming 1% to 1.7% as unbound]), based on these data, it is believed that subjects treated with the top clinical dose of canagliflozin (300 mg) will experience only modest inhibition of systemic SGLT1-mediated glucose uptake (21% inhibition predicted at C_{max} for the 300 mg dose).

3.4.2. Additional Mechanism with Higher Canagliflozin Doses: Inhibition of Gut SGLT1 Glucose Transport

As discussed in Section 1.2, Mechanism of Action, canagliflozin is a potent and selective SGLT2 inhibitor; during drug dissolution prior to drug absorption, gastrointestinal tract luminal

concentrations of canagliflozin may be sufficiently high to inhibit gut wall SGLT1 (an important intestinal glucose transporter), thereby reducing the rate of glucose absorption. In initial Phase 1 studies, reductions in post-meal glucose excursion were detected after pre-meal administration of canagliflozin doses of >200 mg that was not accounted for by differences in UGE (with higher relative to lower doses) suggesting that the 300 mg dose may directly reduce the rate of gut glucose absorption. Two subsequent Phase 1 mechanism of action studies confirmed observations from these earlier Phase 1 studies. Study DIA1022 used dual tracers (^{3}H-glucose infused and ^{14}C-glucose glucose orally administered) to examine the rate of appearance of exogenous (ingested) glucose in healthy volunteers. This study showed that a canagliflozin dose of 300 mg qd reduced the rate of exogenous glucose appearance over the initial 2 hours after meal administration (Figure 3), with increased glucose absorption after 2 hours, so that there was no meaningful reduction in overall absorption of meal glucose over 6 hours. In a separate 28-day Phase 1 study (DIA1007), subjects with T2DM treated with canagliflozin 300 mg twice daily did not exhibit signs of glucose malabsorption as assessed by a hydrogen breath test following an oral glucose challenge (an established method of detecting carbohydrate malabsorption).

Figure 3: Rate of Exogenous Glucose Appearance of Orally Administered Glucose During MMTT in Study DIA1022



Study DIA1045 in subjects with T2DM showed that pre-meal administration of canagliflozin 300 mg (but not 150 mg) provided a greater reduction in the glucose excursion after a mixed meal tolerance test (MMTT) than could be accounted for by the increased UGE.

These studies confirmed that canagliflozin at a dose of 300 mg reduces the rate of glucose absorption, lowering post-meal glucose concentrations, without inducing glucose malabsorption.

3.5. Pharmacokinetic/Pharmacodynamic Relationships

In healthy subjects, canagliflozin decreased RT_G in an exposure-dependent manner, with similar exposure-response relationships observed in both Western and Japanese subjects. In a pooled analysis of data from studies in subjects with T2DM, IC_{50} was estimated to be 32.4 ng/mL

(corresponding with a 90% effective concentration [EC_{90}] of 291.6 ng/mL) and the maximal decrease in RT_G was approximately 67%. It is not currently known why the maximal decrease in RT_G is limited to approximately 67%, but could reflect the activity of other transporters (non-SGLT2) (Liu 2012).

The site of action of canagliflozin inhibiting the SGLT2 transporter in vivo is not established; however, this most likely reflects action in the tubular lumen, due to unbound filtered drug. Canagliflozin is highly protein bound (approximately 99%) and it is expected that only the free (unbound) drug fraction filtered at the glomerulus—consistent with the finding of only a small amount of urinary excretion of parent drug. With filtered unbound drug, the expected concentrations of canagliflozin in the lumen of the proximal tubule (which cannot be readily measured) would be roughly similar to the unbound concentrations in plasma. Based upon PK/PD modeling, the estimated in vivo IC_{50} values for canagliflozin effects on RT_G of 21 ng/mL (in healthy subjects) to 32 ng/mL (in subjects with T2DM) were adjusted for protein binding (using a typical value of 99%), the resulting EC_{50} values based on free (unbound) canagliflozin concentrations were 0.21 to 0.32 ng/mL (0.5 to 0.7 nM), which are below the estimated in vitro IC_{50} value of 4.2 nM. One potential explanation for the estimated in vivo EC_{50} values being somewhat lower than the in vitro IC_{50} value is slow dissociation of canagliflozin from SGLT2, leading to pharmacodynamics effects that are greater than anticipated based solely on the free drug concentration in plasma (although the binding of canagliflozin to SGLT2 is reversible, the dissociation rate is relatively slow, with a half-time of dissociation of 62.1 minutes). Overall, these data are generally compatible with the hypothesis that unbound canagliflozin is filtered by the glomerulus and acts on the luminal side of the proximal tubule cells to inhibit SGLT2-mediated renal glucose reabsorption.

4. PHASE 2 AND 3 CLINICAL DEVELOPMENT

The canagliflozin clinical program was designed to assess the safety and efficacy of canagliflozin in patients with T2DM. To date, the program includes efficacy and safety data from 10,285 subjects (who received at least 1 dose of double-blind study drug) in 9 Phase 3 studies and 1,210 subjects in 3 Phase 2 studies. Of the 10,285 subjects in the Phase 3 program, 3,092 subjects were treated with canagliflozin 100 mg qd and 3,462 subjects were treated with canagliflozin 300 mg qd.

Doses of up to 600 mg per day (as 300 mg bid) were evaluated in Phase 2 trials. Phase 1 studies examining exposure-pharmacodynamic responses and a Phase 2b dose-range finding study in subjects with T2DM (DIA2001) supported selection of doses of canagliflozin of 100 mg and 300 mg for Phase 3 development.

The safety and efficacy of canagliflozin was evaluated in the Phase 3 program in a broad population of T2DM subjects as described below.

4.1. Dose and Dose Regimen Selection

The Phase 1 study in subjects with T2DM (NAP1002) demonstrated that canagliflozin doses of 100 mg qd and greater provided effective reduction in the 24-hour glucose profiles relative to

placebo, supporting progression to the Phase 2b dose-range finding study (DIA2001). As discussed in Section 3.4.1, these Phase 1 studies showed that the 300 mg dose of canagliflozin provided near maximal or maximal lowering of the RT_G over the 24 hour dosing interval, while the 100 mg dose of canagliflozin provided maximal reductions over the first 13 hours, with lesser but still substantial reductions over the remaining 24 hour dosing interval (Figure 2, Section 3.4.1).

In DIA2001 (examining qd doses of 50-, 100-, 200-, and 300 mg, and 300 mg bid), all canagliflozin doses significantly reduced HbA_{1c} and FPG, with the 100 mg qd and 300 mg qd doses providing placebo-subtracted least squares (LS) mean changes from baseline of -0.51% and -0.71% in HbA_{1c}, respectively, and of -25.2 and -32.4 mg/dL (-1.4 and -1.8 mmol/L) in FPG, respectively ($p<0.001$ for comparisons to placebo for both doses). Maximal reductions in HbA_{1c} were seen with the 300 mg qd dose that were numerically larger than with lower doses, and with no further HbA_{1c}-lowering response with the 300 mg bid dose. Thus, the results of the dose-range finding study were consistent with predictions based upon Phase 1 pharmacodynamic results.

As an additional consideration in the selection of the canagliflozin 300 mg qd dose, the effect of this dose on reducing post-meal glucose absorption and glucose excursions (see Section 3.4.2), without inducing glucose malabsorption, suggested this dose would provide additional glycemic benefits.

Based upon the appropriate safety and tolerability observed with canagliflozin 100 mg and 300 mg in Phase 2 studies, and the near maximal glycemic efficacy with canagliflozin 100 mg and maximal glycemic efficacy with canagliflozin 300 mg, these doses were selected for further development in Phase 3 studies. In the Phase 3 studies, canagliflozin was administered prior to the first meal of the day so as to utilize the improvement in post-meal glucose excursion with pre-meal administration of canagliflozin 300 mg.

4.2. Overview of Phase 2 and 3 Program Design

The safety and efficacy of canagliflozin were studied in 9 double-blind, controlled Phase 3 clinical studies across a broad population of subjects with T2DM, providing an extensive experience with this agent. Both active-controlled and placebo-controlled studies were conducted. The Phase 3 program included studies requiring specific background treatments for diabetes done in an otherwise general T2DM population and studies in which canagliflozin was added to any ongoing diabetes treatment regimen in special, selected populations. Table 4 provides the background diabetes treatments, study durations, and study sample sizes for each Phase 3 study.

Supportive analyses also included 1,210 subjects enrolled in three 12-week Phase 2 studies. In one placebo-controlled Phase 2b dose-range finding study (DIA2001), subjects 18 to 65 years of age with T2DM who had not achieved optimal glycemic control while receiving near maximal effective doses of metformin were exposed to canagliflozin at doses of 50 mg, 100 mg, 200 mg or 300 mg qd; canagliflozin 300 mg bid; sitagliptin 100 mg qd; or placebo bid. A second

placebo-controlled, dose-range finding study (TA-7284-04) conducted by the sponsor's collaborator, Mitsubishi Tanabe Pharma Corporation, in adults from Japan with T2DM, evaluated canagliflozin (50 mg, 100 mg, 200 mg, 300 mg qd) as monotherapy. The third Phase 2 study (OBE2001), conducted by the sponsor, enrolled non-diabetic overweight and obese subjects 18 to 65 years of age with baseline BMI 30 to <50 kg/m2 (or a BMI 27 to <50 kg/m^2 in the presence of hypertension and/or dyslipidemia) treated with canagliflozin 50 mg, 100 mg or 300 mg qd, or placebo.

Table 4: Phase 3 Double-Blind Studies Providing Evidence for the Efficacy and Safety of Canagliflozin in Subjects with T2DM

Study / Population (HbA_{1c} Inclusion Criterion) (number of centers/status)	**Background Therapy**	**Design/Duration**[a]	**Number of Randomized Subjects**	**Study Treatment Groups**
Phase 3 Placebo–Controlled Studies				
DIA3005 (general T2DM) *Main Study* (HbA_{1c} ≥7.0% to ≤10.0%) (90 centers/ completed)	Diet/exercise	Placebo-controlled 52 weeks double-blind (26 weeks core/26 weeks extension period)	N=587 (excluding high glycemic cohort)	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg
High Glycemic Cohort (HbA_{1c} >10.0% to ≤12.0%) (40 centers/ completed)	Diet/exercise	26 weeks double-blind (26 weeks core / no extension)	N=91	1) Canagliflozin – 100 mg 2) Canagliflozin – 300 mg
DIA3002 (general T2DM) (HbA_{1c} ≥7.0% to ≤10.5%) (85 centers/ completed)	Metformin[d] and SU[d]	Placebo-controlled 52 weeks double-blind (26 weeks core/26 weeks extension period)	N=469	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg
DIA3006[b] (general T2DM) (HbA_{1c} ≥7.0% to ≤10.5%) (169 centers/ completed)	Metformin[d]	Placebo- and active-controlled 52 weeks double-blind (26 weeks core/26 weeks extension period)	N=1284	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg 4) Sitagliptin – 100 mg
DIA3012 (general T2DM) (HbA_{1c} ≥7.0% to ≤10.5%) (74 centers/ completed)	Metformin[d] and pioglitazone[d]	Placebo-controlled 52 weeks double blind (26 weeks core/26 weeks extension period)	N=344	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg

Table 4: Phase 3 Double-Blind Studies Providing Evidence for the Efficacy and Safety of Canagliflozin in Subjects with T2DM

Study / Population (HbA_{1c} Inclusion Criterion) (number of centers/status)	**Background Therapy**	**Design/Duration**[a]	**Number of Randomized Subjects**	**Study Treatment Groups**
Phase 3 Active–Controlled Studies				
DIA3009 (general T2DM) (HbA_{1c} ≥7.0% to ≤9.5%) (157 centers/ completed)	Metformin[d]	Active-controlled 104 weeks double blind (52 weeks core/52 weeks extension period)	N=1452	1) Canagliflozin – 100 mg 2) Canagliflozin – 300 mg 3) Glimepiride (titrated 1 mg up to a maximum[c] of 6 to 8 mg)
DIA3015 (general T2DM) (HbA_{1c} ≥7.0% to ≤10.5%) (140 centers/ completed)	Metformin[d] and SU[d]	Active-controlled 52 weeks double blind	N=756	1) Canagliflozin – 300 mg 2) Sitagliptin – 100 mg
Phase 3 Studies in Special Populations				
DIA3010 (T2DM / older [≥55 to ≤ 80 years] subjects) (HbA_{1c} ≥7.0% to ≤10.0%) (90 centers/ ongoing)	Any diabetes therapy (diet or oral or parenteral AHA)	**Older Subjects (ie, ≥55 to ≤80 years of age) /Bone Density Evaluation** Placebo-controlled 104 weeks double blind (26 weeks core/78 weeks extension period)	N=716	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg
DIA3004 (T2DM with renal impairment [eGFR ≥30 to <50 mL/min/1.73 m^2]) (HbA_{1c} ≥7.0% to ≤10.5%) (89 centers/ completed)	Any diabetes therapy (diet or oral or parenteral AHA)	**Study in Subjects with Renal Impairment** Placebo-controlled 52 weeks double-blind (26 weeks core/26 weeks extension period)	N=272	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg

Table 4: Phase 3 Double-Blind Studies Providing Evidence for the Efficacy and Safety of Canagliflozin in Subjects with T2DM

Study / Population (HbA_{1c} Inclusion Criterion) (number of centers/status)	**Background Therapy**	**Design/Duration**[a]	**Number of Randomized Subjects**	**Study Treatment Groups**
DIA3008 (CANVAS) (T2DM with CV disease or at high risk for CV disease) (HbA_{1c} ≥7.0% to ≤10.5%) (369 centers/ ongoing) Insulin substudy (316 centers/ completed) Sulphonylurea substudy (80 centers/ completed)	Any diabetes therapy (diet or oral or parenteral AHA) **Substudies:** On insulin (≥20 units/day On SU agent[d](defined doses)	**Cardiovascular Study – Including 2 Efficacy and Safety Substudies (Insulin; SU)** Placebo-controlled, double-blind Event-driven; estimated duration of 4 to 8 years Duration of efficacy substudies: 18 weeks	N=4330 (total)	1) Placebo 2) Canagliflozin – 100 mg 3) Canagliflozin – 300 mg

[a] All studies were multicenter, parallel-group studies; all canagliflozin doses are once-daily
[b] Study DIA3006 was both placebo- and active controlled.
[c] The maximum dose allowed based on the approved country-specific label
[d] Metformin at a dose of ≥ 2000 mg/day (or ≥ 1500 mg/day, if unable to tolerate a higher dose); SU at maximally or near maximally effective doses (specified in the protocol); pioglitazone 30 or 45 mg/day

4.2.1. Phase 3 Study Designs

Studies included monotherapy use (DIA3005), and combination use as add-on to metformin (DIA3006 and DIA3009), as add-on to metformin/pioglitazone (DIA3012), and as add-on to metformin/SU (DIA3002 and DIA3015). Three special population Phase 3 studies examined canagliflozin as add-on to current diabetes treatments (discussed below). Pre-specified 18-week substudies of one of these special population studies, the CV safety study (DIA3008), examined combination use of canagliflozin as add-on to SU and as add-on to insulin.

In the Phase 3 studies examining specific uses (monotherapy or specific AHA combinations), eligible subjects already receiving protocol-specified diabetes therapy (Table 4) entered a 2-week, single-blind, placebo run-in period. If all enrollment criteria were met (see below) at the end of this run-in period, these subjects were randomly assigned to double-blind treatment on Day 1. Subjects entering these studies not yet receiving the protocol-specified background diabetes treatment (agents or dose of agents) at screening underwent an AHA adjustment and dose-stabilization period during which the background AHA therapy was initially adjusted to meet study-specific criteria followed by a dose stable period (at least 8 weeks). If all enrollment criteria were met at the end of this run-in period, subjects were randomly assigned to double-blind treatment on Day 1.

Three Phase 3 studies were conducted as add-on to current diabetes therapy. Study DIA3010 assessed efficacy and safety in older subjects (≥ 55 to ≤ 80 years) with T2DM; study DIA3004 was designed to evaluate efficacy and safety of canagliflozin in T2DM subjects with renal impairment as defined by eGFR ≥30 to <50 mL/min/1.73 m^2 (eGFR limits, as requested by the Food and Drug Administration [FDA]); and study DIA3008 included subjects with or at high risk of CV disease. The design of these 3 studies required subjects to be on a stable diabetes treatment regimen (diet/exercise or any approved AHAs alone or in combinations) for at least 8 weeks prior to study entry.

Across Phase 3 studies, male and female subjects ages ≥18 and ≤80 years (with no upper age limit in study DIA3004 and DIA3008) with inadequately controlled T2DM were eligible. Subjects were required to have an HbA_{1c} level of ≥7.0% and ≤10.5% (≤10.0% in the DIA3005 monotherapy study main study) while on a stable regimen of their diabetes therapy (at least 8 weeks). Subjects with diabetic ketoacidosis, type 1 diabetes mellitus, an alanine aminotransferase (ALT) level >2.0 times the ULN or total bilirubin >1.5 times the ULN at screening were not eligible to enroll in these studies. Other than in Study DIA3004 (renal impairment), subjects with an eGFR value <55 mL/min/1.73 m^2 (or <60 mL/min/1.73 m^2 if based upon restriction of metformin use in the metformin local label) (DIA3002, DIA3006, DIA3009, DIA3012, DIA3015) or <50 mL/min/1.73 m^2 (DIA3005, DIA3008, DIA3010) were also not eligible.

Randomization, Treatments, and Double-blind Period Duration

All studies included both canagliflozin doses (100 mg and 300 mg) with the exception of DIA3015, which included only the 300 mg dose. The specific active comparator AHA included in DIA3009 and DIA3015 was glimepiride and sitagliptin, respectively; DIA3006 also included

an active control (sitagliptin) in addition to the placebo control. The doses of these comparator drugs used in the Phase 3 studies were consistent with their product labeling (including titration to glycemic goal for glimepiride in DIA3009).

Randomization to double-blind study treatment was blinded to sponsor staff, investigators, center personnel, subjects; sponsor staff involved in the study remained blinded until after all subjects completed the primary study time point, and the database lock was completed, however, investigators, center personnel, and subjects remained blinded until study completion. Subjects in the Phase 3 studies were to remain on stable doses of the diabetes treatment (diet/exercise or AHA regimen) established at the start of the run-in period throughout the double-blind treatment period. Subjects whose hyperglycemia met progressively stricter pre-specified criteria (based upon repeated and confirmed FPG through Week 26, and HbA_{1c} after Week 26, see below) were treated with protocol-specified rescue AHA medication, and continued in the study. No rescue was provided in Study DIA3015—subjects in this study who met the criteria below were discontinued.

Time Point	Value
After Day 1 through Week 6	FPG >270 mg/dL
After Week 6 through Week 12	FPG >240 mg/dL
After Week 12 through Week 26	FPG >200 mg/dL
After Week 26	HbA_{1c} >8.0%

Double-blind Extension Period

In all studies except DIA3015, the DIA3005 high glycemic substudy, and the DIA3008 substudies, subjects who completed the primary assessment time point continued to receive double-blind study treatment during a subsequent double-blind extension period. The double-blind treatment received during the extension period was the same as that assigned at randomization in study DIA3002 (add-on to metformin/SU); in studies DIA3005, DIA3006, and DIA3012, to avoid prolonged placebo treatment, subjects assigned to placebo were switched to an active agent at Week 26 to maintain blinding. The DIA3005 high glycemic substudy completed at Week 26. DIA3008 is an event-driven study; subjects in the 18-week substudies of DIA3008 continued in this trial.

4.3. Study Assessments

The study visits generally occurred approximately every 6 weeks during the double-blind period up to the study-specific primary endpoint (at 18 weeks for the DIA3008 substudies, at 26 weeks for all other placebo-controlled studies, and 52 weeks for the active-controlled studies), after which the between-visit interval was modestly longer. The efficacy measurements included laboratory assessments (HbA_{1c}, FPG, fasting C-peptide, insulin and proinsulin and lipids, free fatty acids) and procedures (MMTT, frequently sampled [FS]-MMTT, body weight, waist circumference, blood pressure (BP), dual energy X-ray absorptiometry (DXA), and computed tomography (CT) scan [abdominal]).

For all of the Phase 3 studies, safety evaluations included the collection of adverse events, safety laboratory tests (hematology, chemistry [serum creatinine, eGFR (calculated using the Modification of Diet in Renal Disease formula [MDRD], urinalysis, and albumin-to-creatinine ratio in first morning urine collection in selected studies), centrally-read 12-lead electrocardiograms (ECGs), vital signs (BP and pulse rate), body weight, physical examinations, self-monitored blood glucose and assessment of potential hypoglycemic episodes (eg, from the subject diary provided to subjects).

In study DIA3010 (in subjects ≥55 and ≤80 years of age), bone mineral density (BMD) was assessed at the lumbar spine, hip, and distal forearm using DXA. Serum beta collagen type 1 carboxy-telopeptide (beta-CTx) and propeptide amino terminal of type I procollagen (P1NP) were measured in this study through 26 weeks; based upon DXA findings, additional biomarkers were assessed including serum beta-CTx at Week 52, osteocalcin at Weeks 26 and 52, and serum PTH at Weeks 26 and 52. In study DIA3009 (active-comparator [glimepiride] controlled add-on to metformin study), DXA was performed to assess body composition fat, lean and bone mineral content; total body BMD was also assessed.

An Independent Data Monitoring Committee (IDMC), which included 2 diabetologists (1 serving as chairperson), 2 cardiologists, 2 statisticians, and a urologic oncologist, monitored unblinded analyses of serious adverse events and specific CV events at specific regular intervals (based on the canagliflozin program IDMC charter) across the entire clinical development program for canagliflozin, with the authority to recommend specific program-wide decisions to the sponsor. All IDMC physician members are experienced in clinical studies, but did not participate in the canagliflozin studies.

Several independent Endpoint Adjudication Committees (EACs) were empanelled to assess several types of events. All EACs worked under the dedicated charters and an established set of standard operating procedures, including reviews blinded to treatment group assignments. These EACs included:

- **Cardiovascular Endpoint Adjudication Committee (CVEAC)**: The role of the CVEAC was to provide an independent assessment of events potentially consistent with a "MACE-plus" (major adverse CV events [CV death, non-fatal myocardial {MI}, non-fatal stroke] plus events of hospitalized unstable angina), as identified by the investigator. In addition, the sponsor's medical monitoring staff reviewed blinded events on a regular basis from the clinical database and alerted the investigator to potential events not identified by the investigator. Database preferred-term searching was used to augment the sponsor's review of potential study endpoints. The assessed events included CV death/all deaths, non-fatal myocardial infarction, non-fatal stroke, hospitalized unstable angina, hospitalized congestive heart failure (CHF), and venous thromboembolism (VTE). The committee consisted of physicians with clinical and research experience, and expertise in the specialty areas for adjudication. The purpose of this CVEAC was to apply pre-specified definitions to adjudicate and classify the events while blinded to study treatment.
- **Fracture Adjudication Committee (FAC):** The role of the FAC was to provide an independent assessment, verification and classification of bone fractures. The FAC consisted

of physicians/radiologists who adjudicated the bone fractures (either as flagged by the (investigator or as submitted by the sponsor) by location (eg, lower limb) and classified bone fracture type (eg, low trauma, pathological) in a blinded manner. Low trauma fracture was a key safety parameter in the canagliflozin clinical development program.

- **Hepatic Events Assessment Committee (HEAC):** Events meeting pre-specified criteria (see Section 6.10) were evaluated by the HEAC, an external independent group of experts in hepatic disease, who also had experience in hepatic assessment. The HEAC was responsible for categorizing assessed hepatic events according to causality with relationship to study drug, and also to assess other characteristics of the event (type, severity, alternative etiologies, if appropriate).
- **Renal Clinical Events Committee (CEC):** The role of the renal CEC was to provide an independent blinded review for the causality assessment for renal laboratory parameters and other selected renal events based upon pre-specified criteria (see Section 6.4.2.6). The renal CEC consisted of nephrologists with experience in renal adjudication in a clinical trial setting.

5. CLINICAL EFFICACY

5.1. Analysis Methods

All primary and major secondary efficacy analyses for the individual Phase 2 and Phase 3 studies were based on the modified intent-to-treat (mITT) analysis set, defined as all randomized subjects who took at least 1 dose of double-blind study drug. Analyses of the primary efficacy endpoint (HbA_{1c}) were also performed on the completer analysis set and the per protocol (PP) analysis set. The completer analysis set consisted of mITT subjects that completed treatment through the primary time point and did not initiate rescue therapy, and the PP analysis set additionally excluded subjects with major protocol violations that could have affected interpretation of the primary efficacy endpoint. Additional sensitivity analyses of major secondary endpoints were performed using the completer analysis set.

The last observation carried forward (LOCF) approach, as outlined in the FDA's guidance on the development of new drugs for T2DM (FDA 2008), was used to impute missing data for the primary efficacy analysis. As a prespecified sensitivity analyses, the primary efficacy endpoint was analyzed using a mixed model repeated measures analysis based on observed data. A baseline carried forward (BOCF) approach to imputation was also explored as a highly conservative approach towards estimation of the treatment effect. Further post-hoc sensitivity analyses have also been conducted to assess the impact of missing data based on recommendations from the National Research Council's report on The Prevention and Treatment of Missing Data in Clinical Trials (NRC 2010). A pattern mixture model under the assumption of control based pattern imputation was also performed to explore the potential impact of informative censoring.

For analyses of the change from baseline for a given efficacy variable, only subjects who had both baseline and at least 1 postbaseline measurement were included. If a subject was placed on rescue medication during the study, all efficacy data after initiation of rescue therapy were

censored, and the last postbaseline (ie, after initiation of double-blind study drug) value prior to the time of rescue therapy initiation was carried forward. Baseline was defined as the pre-dosing measure on Day 1.

5.1.1. Analysis of Primary Efficacy Endpoint

The protocol-specified primary efficacy endpoint for the Phase 3 studies was the change in HbA_{1c} from baseline to Week 26 for the Placebo-controlled Studies (DIA3002, DIA3004, DIA3005, DIA3006, DIA3010, and DIA3012) or Week 52 for the Active-controlled Studies (DIA3009 and DIA3015). The change in HbA_{1c} from baseline to Week 18 was defined as the primary efficacy endpoint for the 2 glycemic substudies in the DIA3008 study.

In the individual Phase 3 studies, analysis of the change from baseline in HbA_{1c} was performed using an analysis of covariance (ANCOVA) model. In general, the model included terms for treatment and randomization stratification factor(s) (if applicable) as fixed effects and the corresponding baseline HbA_{1c} value as a covariate. Treatment differences between each canagliflozin group and the comparator(s) (either placebo or active-comparator) in the LS means and the 2-sided 95% confidence intervals (CI) were estimated from the model for each individual study. The p-values for testing superiority for HbA_{1c} lowering were calculated by comparing the LS means.

A noninferiority margin of 0.3% was used for comparisons of canagliflozin with sitagliptin after 52 weeks of treatment in DIA3015 and with glimepiride after 52 weeks of treatment in DIA3009. The choice of noninferiority margin was based on a meta-analysis of data from relevant literature in concert with clinical judgment as well as with reference to values suggested in the FDA and the European Medicines Agency (EMA) guidances (FDA 2008, EMA 2012) for diabetes. A step-down test of superiority was prespecified based on the closed testing principle if noninferiority on the primary efficacy endpoint was achieved. If the upper limit of the 95% CI for the treatment difference in LS means from the ANCOVA was <0, statistical superiority of canagliflozin compared with the active comparator would be concluded.

Results of the primary and some sensitivity analyses for four studies are presented in Attachment 2.

5.1.2. Analyses of Major Secondary Efficacy Endpoints and Control of Multiplicity

The secondary glycemic efficacy endpoint in the Phase 3 studies was the percentage of subjects achieving a target HbA_{1c} value of <7.0% at the primary assessment time point and change from baseline in fasting plasma glucose. Based upon standard guidances (eg, American Diabetes Association), an HbA_{1c} value of <7.0% is considered as an appropriate glycemic goal in the management of patients with T2DM. Fasting plasma glucose is another important measure of glycemic control, closely correlated with HbA_{1c}. Other secondary efficacy endpoints included in the Phase 3 studies are the change from baseline to the primary assessment time point in body weight, SBP, and fasting plasma lipids. For continuous secondary endpoints, analyses were performed, using an ANCOVA model similar to that described for the primary analysis

(ie, treatment and stratification factor(s) as fixed effects, and the corresponding baseline value as a covariate). Dichotomous variables (eg, proportion of subjects with HbA_{1c} <7.0%) were analyzed using a logistic regression model with treatment and stratification factor(s) (if applicable) as fixed factors and baseline HbA_{1c} as a covariate. Treatment differences in terms of each canagliflozin group minus the comparator (either placebo or active comparator) and 95% CIs for each variable were estimated from the respective model for each individual study.

For each Phase 3 study, a prespecified sequential testing procedure was applied to assessment of the treatment differences of the primary and major secondary efficacy endpoints, strongly controlling the family-wise error rate at 5%. Each study followed a prespecified testing hierarchy, and in some studies, this included 2 families of tests using the Hochberg procedure for endpoints of SBP, HDL-C, and TG, conditional on the statistical significance of the prior test(s). In all placebo-controlled studies, the primary efficacy endpoint was change from baseline in HbA_{1c} for the canagliflozin 300 mg group relative to the placebo group, followed by the change from baseline for the canagliflozin 100 mg group relative to the placebo group. The subsequent testing sequence was study specific (specified in the study protocol), including such endpoints as HbA_{1c} <7%, FPG, body weight, SBP, high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG). For representative examples of the hierarchy of hypotheses testing, see Attachment 3 for the sequential testing procedures used in studies DIA3005 (a placebo-controlled study) and DIA3009 (an active-controlled study). The statistical testing proceeded sequentially conditional on the statistical significance of the prior test(s). If a test did not reach significance, no further formal statistical testing was performed and any p-values associated with subsequent comparisons in the testing sequence were identified as nominal. If an endpoint was not included in the testing sequence, only the 95% CI based on the corresponding ANCOVA model was presented.

5.2. Populations Supporting Efficacy: Disposition, Baseline Characteristics, and Exposure

5.2.1. Individual Studies

Phase 3 studies, or substudies, were conducted in support of use in monotherapy, add-on to metformin, add-on to SU, add-on to metformin and SU, add-on to metformin and pioglitazone, and add-on to insulin (alone or in combination with other AHAs); see Table 4 above for additional study design information.

Detailed information on the disposition of each Phase 3 study is summarized in Attachment 4. Detailed information on the key baseline demographic, anthropometric and diabetic characteristics of subjects comprising the mITT analysis sets (defined as all randomized subjects who took at least 1 dose of double-blind study medication) are summarized for each Phase 3 study in Attachment 5. Only data for the main study cohort (ie, not including the high glycemic cohort substudy) of the monotherapy study (DIA3005) are shown in this table. A brief cross-study description of baseline characteristics is provided below.

Across the Phase 3 clinical studies included in the canagliflozin NDA providing support for the efficacy of canagliflozin, a total of 7,803 subjects were randomized and received at least 1 dose

of study drug (ie, mITT analysis set) (Attachment 4). This included 4,994 subjects treated with canagliflozin (100 mg or 300 mg), 1,583 treated with placebo, and 1,226 treated with an active comparator (744 sitagliptin, 482 glimepiride).

Disposition in Individual Studies

Overall, a high proportion of subjects in each Phase 3 study completed the double-blind treatment period through the primary assessment time point (Attachment 4). The proportions of subjects completing each study differed, in part, as a function of treatment duration.

The completion rate in the canagliflozin treatment groups for studies having a primary assessment time point at Week 18 (DIA3008 insulin and DIA3008 SU substudies) was approximately 93% and the completion rates at Week 26 ranged from 80% to 90% (studies DIA3005, DIA3006, DIA3002, DIA3012, DIA3004, and DIA3010), and were similar for both canagliflozin doses. In the 2 studies having a Week 52 primary assessment time point, the completion rate in the canagliflozin groups was approximately 75% in study DIA3009 and approximately 67% for study DIA3015; in the sitagliptin treatment group in study DIA3015, the completion rate was approximately 56%. Note that in study DIA3015, subjects meeting protocol-specified glycemic discontinuation criteria were withdrawn from the study (rather than receiving rescue therapy), which led to the lower completion rate in study DIA3015 compared to the other Phase 3 studies. In this study, 22.5% of subjects in the sitagliptin group, and 10.6% of subjects in the canagliflozin group were withdrawn due to meeting glycemic discontinuation criteria. The completion rate in DIA3015 is consistent with that previously reported in a 52-week study with sitagliptin (Nauck 2007), including a similar rate of discontinuations due to non-glycemic criteria.

In all placebo-controlled Phase 3 studies, except the DIA3008 SU substudy and DIA3004 renal impairment study, the percentage of subjects who discontinued double-blind treatment prior to the primary assessment time point was lower for the canagliflozin treatment groups than for the placebo group. In the 52-week active-controlled studies, the overall discontinuation rates in the canagliflozin groups were comparable to those observed for glimepiride (in DIA3009), and lower than sitagliptin 100 mg (in DIA3015).

Across all Phase 3 studies (except DIA3015 which did not include glycemic rescue criteria), a small proportion of subjects treated with canagliflozin received glycemic rescue, and ranged from 0 to 5% in the 26-week placebo-controlled studies (and 18-week substudies) and was approximately 6% in combined canagliflozin groups in the 52-week active-controlled study, DIA3009. In contrast, a higher proportion of subjects on placebo or comparator received glycemic rescue: ranging from 9 to 23% in the placebo-controlled studies, and 10.5% in glimepiride treatment group in DIA3009.

Summary statistics for subjects included in the mITT analysis set, proportion subjects discontinued and proportion of subjects who received rescue therapy prior the primary endpoint is provided for each Phase 3 study in Attachment 4.

Baseline Characteristics

Demographic

The median age of subjects in most Phase 3 studies was in the 55- to 60-year range. The median age of subjects in DIA3004 and the DIA3008 substudies was in the 60- to 69-year range, which was anticipated based upon entry criteria that required diabetes comorbidities (eg, renal impairment in DIA3004 and CV disease or high risk for CV disease in DIA3008). The median age was also older in DIA3010 (63 years) as this study focused on older subjects with T2DM. A similar frequency distribution for the various age ranges was seen for subjects treated with placebo or active comparators in the Phase 3 studies.

There was a modestly higher proportion of males compared with females for the DIA3008 substudies, DIA3004, and DIA3012, and an approximately equal distribution of both sexes for the other Phase 3 studies. Whites represented the most common racial group in all studies (64% to 83%). However, there was substantial representation of Asian subjects, with a smaller representation of black or African-American subjects (Note: the majority of the approximately 359 black or African-American subjects were recruited from the United States [US] across all Phase 3 studies and represent approximately 14% of the subjects randomized from the US, consistent with the proportion having T2DM in the US in this population). About 16% of subjects recruited both worldwide and 17% in the US were of Hispanic or Latino ethnicity.

Anthropometric and Diabetes Disease Characteristics

A high proportion of subjects were overweight (World Health Organization [WHO] 1997), and in all studies, other than the DIA3008 SU substudy, a majority of subjects were obese having a baseline BMI of 30 kg/m^2 or greater. The mean baseline HbA_{1c} values ranged from 7.7% to 8.4% across studies or substudies. The high glycemic substudy, conducted as part of the monotherapy study (DIA3005), had a higher mean baseline HbA_{1c} (10.6%), consistent with inclusion criteria (HbA_{1c} >10 to ≤12%).

Subjects in the monotherapy study (DIA3005) had the shortest median disease duration (3 years) across the Phase 3 studies. Subjects in the metformin monotherapy studies (DIA3006 and DIA3009) had a moderate disease duration (median of approximately 5 to 6 years), and subjects in the add-on studies to dual combination therapy (DIA3002, DIA3015, and DIA3012) had a longer disease duration (median of approximately 8 to 10 years). Subjects in the DIA3008 insulin substudy and DIA3004 had the longest duration of disease (median of approximately 15 years), consistent with the time to progression of disease leading to the requirement for the use of insulin therapy or development of diabetic nephropathy.

The proportion of subjects with diabetes microvascular complications generally mirrored the disease duration. Baseline eGFR reflected diabetes duration, study enrollment criteria (to be consistent with the metformin label), and subject median age across studies.

5.2.2. Pooled Populations for Additional Efficacy Analyses: Assessment of Impact of Baseline Factors, and Assessment of Efficacy in Renal Impairment

Two pooled populations were created for further assessments of efficacy: the pooled population of placebo-controlled studies and the pooled population of subjects with renal impairment.

The pooled population of placebo-controlled studies included subjects from all studies (and substudies) that supported specific uses of canagliflozin (eg, in monotherapy, or in add-on combination uses, or in add-on to insulin use; see Section 4.2) and was created to provide a detailed assessment of the consistency of efficacy responses (HbA_{1c}-lowering and body weight reduction) by baseline subgroup factors (eg, demographic [such as race, ethnicity], anthropometric [such as age, sex], disease-related characteristics [such as BMI, baseline HbA_{1c}, baseline eGFR]).

The pooled population of subjects with renal impairment (using National Kidney Foundation definition of Stage 3 renal insufficiency, eGFR 30 to <60 mL/min/1.73 m^2) was used to provide an additional assessment of efficacy (HbA_{1c}-lowering and body weight changes) in this important group of patients. This pooled population drew from 4 Phase 3 studies (the dedicated study in subjects with renal impairment [DIA3004]; and 3 other studies that included subjects with this range of eGFR: the monotherapy study [DIA3005], the study in older subjects with T2DM [DIA3010], and the CV study [DIA3008]).

In this pooled renal impairment population (baseline eGFR of ≥30 to <60 mL/min/1.73 m^2), there were a total of 1,085 treated (mITT) subjects from 4 Phase 3 studies (with inclusion criteria allowing subjects with eGFR <60 mL/min/1.73 m^2). This included 338 subjects on canagliflozin 100 mg, 365 subjects on canagliflozin 300 mg and 382 subjects on placebo. Mean eGFR in this population was 48.2 mL/min/1.73 m^2 and similar across treatment groups (47.8 to 48.8 mL/min/1.73 m^2). Median eGFR was 50.0 mL/min/1.73 m^2 (49.1 to 51.0 mL/min/1.73 m^2) with about one third of the subjects with baseline GFR 30 to <45 mL/min/1.73 m^2. Almost all subjects (95%) in the pooled renal impairment population were receiving background AHA therapy at baseline, with biguanides (ie, metformin) (34%) and SU agents (40%) being the most common oral AHAs. At baseline, basal (ie, long-acting) and bolus (ie, fast-acting) insulin was used in combination in 39% of subjects in this population, with 15% and 6% of subjects using basal or bolus insulin alone, respectively (see Section 6.1.2 for additional demographic and anthropometric baseline characteristics).

Results from the analyses of the impact of subgroup factors on efficacy are presented in Sections 5.3.2 and 5.7, respectively.

5.3. Glycemic Efficacy in Monotherapy or Add-on Combination Treatment

5.3.1. Individual Studies

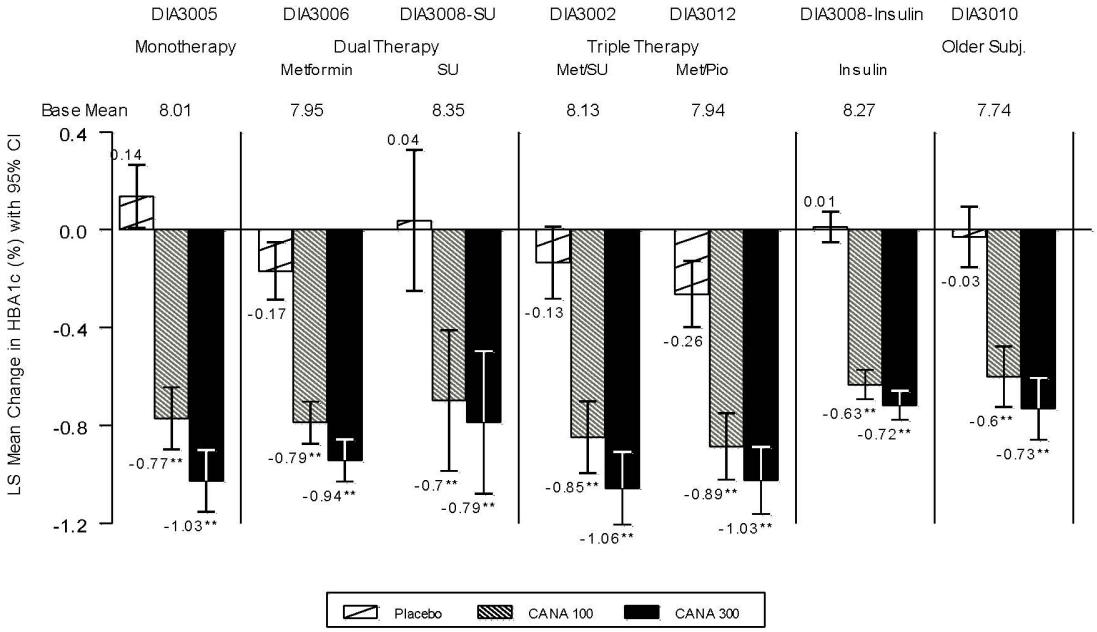
Placebo-controlled Studies (other than the DIA3004 Renal Impairment Study)

Reduction in HbA_{1c} and Proportion to HbA_{1c} Goal

Canagliflozin was effective in reducing HbA_{1c} in a broad range of subjects, both as monotherapy and when given in dual combinations (adding on to metformin or to SU agents), in triple oral AHA combinations (adding on to metformin plus an SU agent or metformin plus pioglitazone) and in combinations with insulin (alone or with other agents). The placebo-controlled studies/substudies demonstrated that both canagliflozin 100 mg and canagliflozin 300 mg were superior to placebo in HbA_{1c}-lowering.

The largest placebo-subtracted LS mean reductions in HbA_{1c} at the primary assessment time point were observed in the monotherapy study (-0.91% and -1.16% with the canagliflozin 100 mg and 300 mg groups, respectively). The HbA_{1c}-lowering efficacy of canagliflozin across the add-on studies (add-on to AHA monotherapy, add-on to dual AHA combination therapy, add-on to insulin, and add-on to standard of care) was generally consistent, with the canagliflozin 100 mg group providing a reduction in HbA_{1c} relative to the placebo group ranging from -0.57% to -0.74%, and with the canagliflozin 300 mg group providing a reduction in HbA_{1c} relative to the placebo group ranging from -0.70% to -0.92%. The LS mean changes from baseline in HbA_{1c} at the primary assessment time point in the Placebo-controlled Phase 3 studies (or substudies) are presented in Figure 4.

Figure 4: HbA_{1c} (%): LS Mean Changes From Baseline at Primary Assessment Time Point: Study-by-Study Comparison of Placebo-controlled Phase 3 Studies

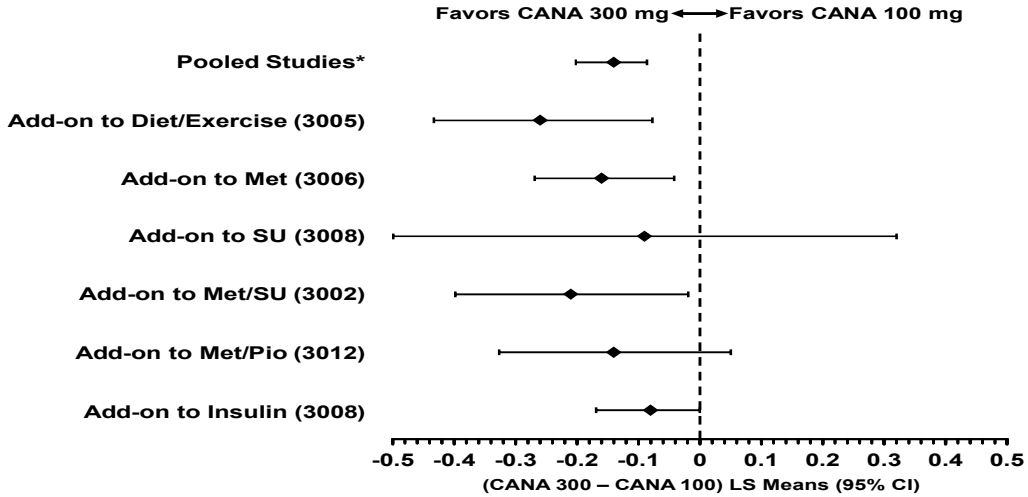


** Statistically significant ($p<0.001$) vs placebo based on the ANCOVA models from individual studies.
Note: LOCF; mITT analysis set
Note: Data for DIA3008 SU substudy is presented for subjects on protocol-specified doses of SU monotherapy regardless of stratification. Data for DIA3008 Insulin substudy is presented for subjects receiving insulin dose ≥30 IU/day.

Across all studies/substudies, a larger HbA_{1c}-lowering response was seen with canagliflozin 300 mg relative to canagliflozin 100 mg, with observed incremental differences in the placebo-subtracted HbA_{1c} reduction from baseline of approximately 0.25% in the monotherapy study and ranging from 0.09% to 0.21% in add-on combination and add-on to current therapy studies (Figure 5).

In addition to the above described studies, a substudy of the monotherapy study (DIA3005) was conducted in subjects whose HbA_{1c} values were too high to qualify for the main study: HbA_{1c} >10.0% to ≤12.0%, but who met all other enrollment criteria. In this substudy, only active treatment was provided (both doses of canagliflozin, no placebo). The LS mean changes from baseline to Week 26 in HbA_{1c} (LOCF) were -2.13% and -2.56% for the canagliflozin 100 mg and 300 mg groups, respectively. These reductions were consistent with the subgroup analysis of the DIA3005 Main Study by baseline HbA_{1c} which demonstrated substantially greater HbA_{1c} lowering in subjects with the highest baseline levels.

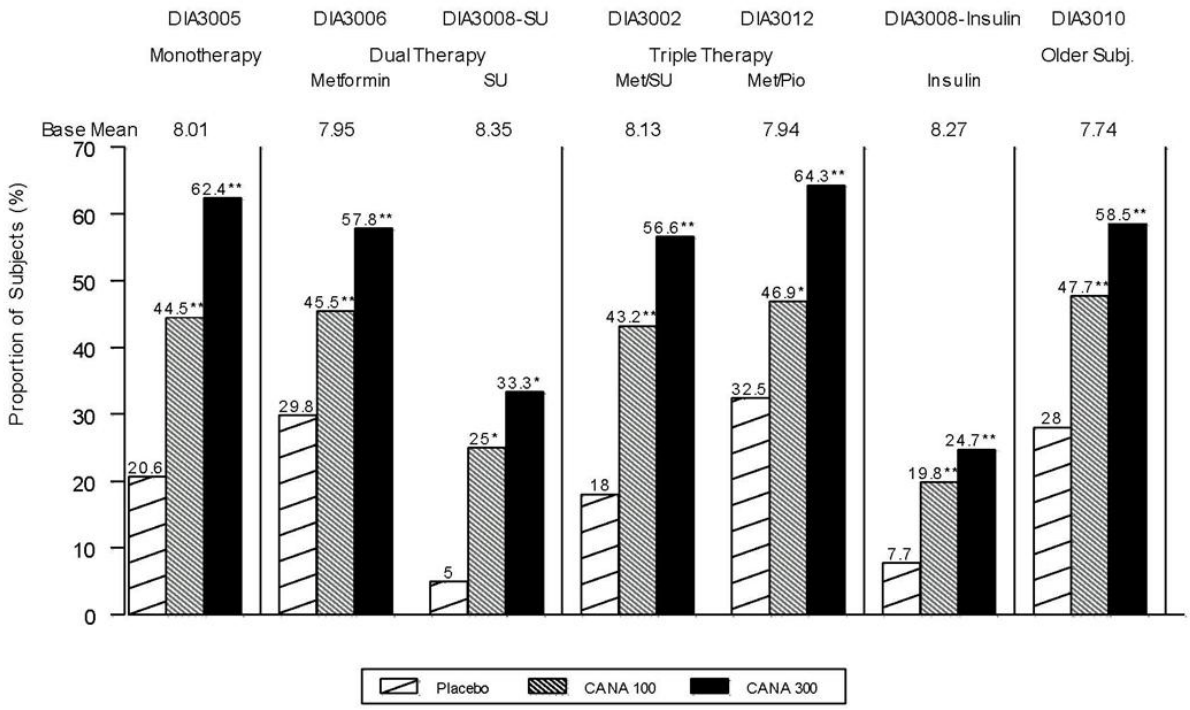
Figure 5: HbA_{1c} (%) Pairwise Comparison of LS Mean Changes From Baseline at Primary Assessment Time Point: Study-by-Study Comparison of Placebo-controlled Phase 3 Studies



* Includes monotherapy, dual therapy, (excluding active comparator group) triple therapy and insulin add-on studies. Based on ANCOVA models, data prior to rescue (LOCF)

In the placebo-controlled Phase 3 studies/substudies, the number of subjects reaching the HbA_{1c} target of <7.0% was greater in the canagliflozin groups compared with the placebo group, and the difference relative to placebo was statistically significant for the canagliflozin 100 mg and 300 mg groups across studies (Figure 6). The treatment effect for canagliflozin in the proportion of subjects reaching the HbA_{1c} target was larger in each Phase 3 study for the 300 mg dose than for the 100 mg dose.

Figure 6: Proportion of Subjects With HbA_{1c} <7.0% at Primary Assessment Time Point: Study-by-Study Comparison of Placebo-controlled Phase 3 Studies

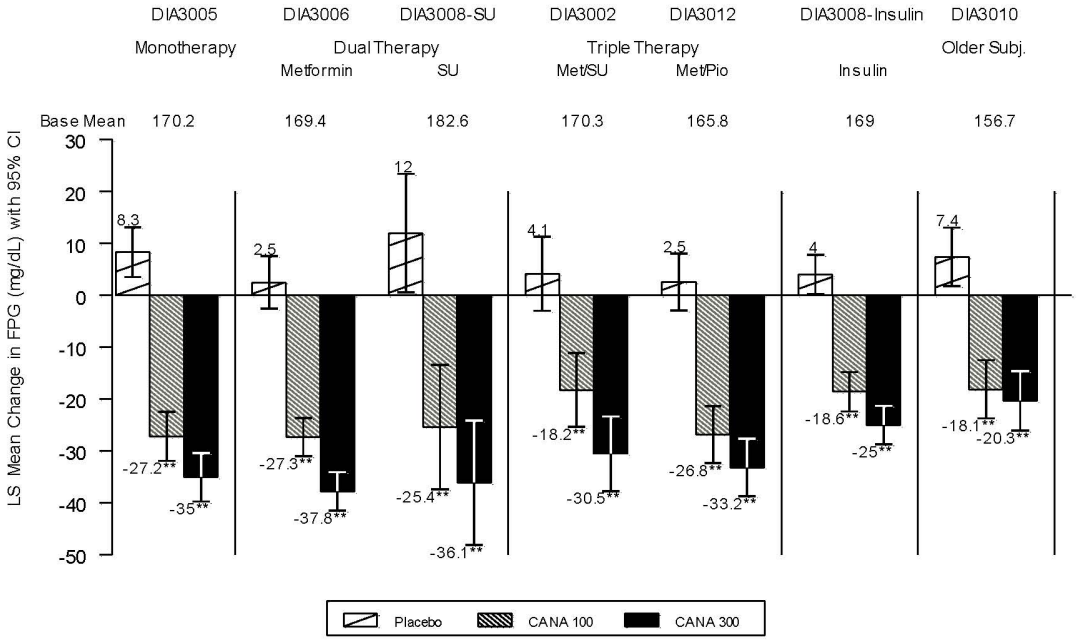


**Statistically significant ($p<0.001$) [(*$p<0.05$)] vs placebo based on the logistic regression from individual studies.
Note: LOCF; mITT analysis set

Reductions in Fasting Plasma Glucose and Post-prandial Glucose

In the placebo-controlled studies/substudies, substantial placebo-subtracted LS mean reductions in FPG were seen with both the 100 mg dose (ranging from -22.4 to -37.4 mg/dL) and with the 300 mg dose (ranging from -27.7 to -48.1 mg/dL) (Figure 7). As noted for improvements in HbA_{1c}, consistently greater reductions in both FPG and in PPG were seen with canagliflozin 300 mg relative to canagliflozin 100 mg.

Figure 7: Fasting Plasma Glucose (mg/dL) LS Mean Changes from Baseline at Primary Assessment Time Point: Study-by-Study Comparison of Placebo-controlled Phase 3 Studies



** Statistically significant ($p<0.001$) vs placebo based on the ANCOVA models from individual studies.
Note: LOCF; mITT analysis set
Cross-reference: ISE attachment 1.2, FEFF01M_SS

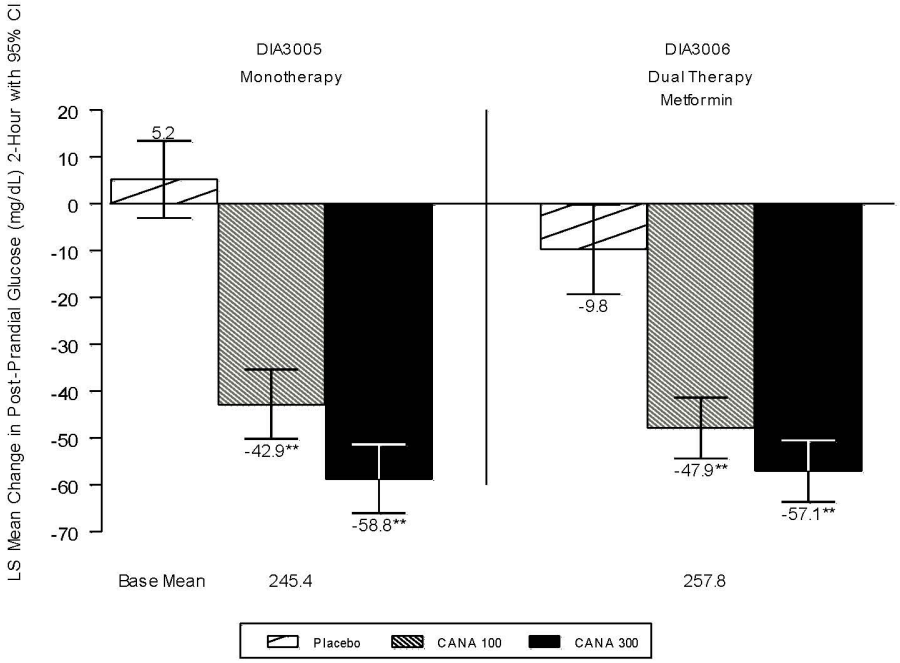
In the monotherapy high glycemic substudy of DIA3005 (monotherapy study), marked LS mean reductions in FPG from baseline to Week 26 of -81.7 mg/dL and -86.3 mg/dL were observed with canagliflozin 100 mg and 300 mg groups respectively.

A consistent observation across the Phase 3 studies was that the maximal or near maximal decrease in FPG from baseline was observed by Week 6 (typically the first postbaseline FPG measurement obtained) in both canagliflozin groups, with generally stable glucose-lowering over the remainder of the double-blind treatment periods. Note that in the Phase 1 studies, rapid improvements in glucose were observed, with substantial glucose reductions observed within hours of dosing in the multiple-dose Phase 1 study in subjects with T2DM (NAP1002). Additionally, substantial 24-hour glucose reductions seen with canagliflozin on Day 1 and further decreases were seen on Day 16.

In the 2 placebo-controlled studies (DIA3005, monotherapy; DIA3006, add-on to metformin) in which all subjects were to have a mixed meal tolerance test, the LS mean reductions in 2-hour postprandial glucose after a standard meal challenge were statistically significant for the canagliflozin 100 mg and 300 mg groups ($p<0.001$ for all comparisons) compared with the placebo group (Figure 8). In both canagliflozin groups, the placebo-subtracted LS mean reduction in the 2-hour PPG was larger than the corresponding reduction in the pre-meal glucose in each study, indicating that the decrease in 2-hour PPG reflects lowering both the pre-meal glucose concentrations (ie, FPG) and the post-meal glucose excursion. In the high glycemic

substudy, LS mean reductions in the 2-hour PPG from baseline to Week 26 of -118.6 mg/dL and -125.8 mg/dL were observed in the canagliflozin 100 mg and 300 mg groups, respectively.

Figure 8: Post-Prandial Glucose (mg/dL): 2-Hour Change From Baseline to Primary Assessment Time Point (Studies DIA3005 and DIA3006)



** Statistically significant ($p<0.001$) vs placebo based on the ANCOVA models from individual studies.
Note: LOCF; mITT analysis set

Placebo-controlled Study in Subjects with Reduced eGFR (DIA3004)

The efficacy of canagliflozin in lowering HbA_{1c} in the study of T2DM subjects with eGFR ≥30 to <50 mL/min/1.73 m^2 was less compared with that seen in other studies, with mean reductions, relative to the placebo group, of -0.30% and -0.40% for the canagliflozin 100 mg and 300 mg groups, respectively (Table 5), both statistically significant.

The proportions of subjects achieving the HbA_{1c} target of <7.0% with canagliflozin 100 mg and 300 mg groups (10% and 15% greater than the placebo group, respectively) was less than that seen in other studies, consistent with the smaller HbA_{1c}-lowering response observed in this study of subjects with T2DM and renal impairment (Table 5).

The LS mean decreases in FPG relative to the placebo group were commensurate with the reductions in HbA_{1c} observed in this study (Table 5).

See Section 5.7 for results in the Pooled Renal Impairment Dataset.

Table 5: Summary of Primary and Major Secondary Efficacy Endpoints at Week 26 in Study DIA3004

Efficacy Endpoint/Statistic	Placebo	CANA 100 mg	CANA 300 mg
HbA_{1c} (%)			
N	87	88	89
Baseline, mean (SD)	8.02 (0.92)	7.89 (0.90)	7.97 (0.81)
Change from baseline, LS mean (SE)	-0.03 (0.09)	-0.33 (0.09)	-0.44 (0.09)
P value (minus placebo) [a]		0.012	<0.001
Diff of LS mean (SE) (minus placebo)		-0.30 (0.12)	-0.40 (0.12)
95% CI[a]		(-0.53;-0.07)	(-0.64;-0.17)
Fasting plasma glucose (mg/dL)			
N	88	90	88
Baseline, mean (SD)	160.83 (43.53)	169.44 (46.37)	158.51 (58.13)
Change from baseline, LS mean (SE)	0.49 (5.09)	-14.89 (5.09)	-11.71 (5.10)
P value (minus placebo) [a]		0.021 [c]	0.069
Diff of LS mean (SE) (minus placebo)		-15.38 (6.64)	-12.20 (6.68)
95% CI[a]		(-28.45;-2.31)	(-25.36;0.96)
% Subjects achieving HbA_{1c} <7.0%			
N	87	88	89
No. (%) subjects achieving HbA_{1c} <7.0%	15 (17.2)	24 (27.3)	29 (32.6)
Diff (%) (minus placebo)		10.0	15.3
95% CI[b]		(-3.3; 23.4)	(1.6; 29.0)
P value (minus placebo)[b]		0.227	0.017[c]

[a] Pairwise comparison: p values and CIs are based on the ANCOVA model with treatment, stratification factors (AHA washout, Atherosclerotic CV Disease History) and adjusting for the corresponding baseline value and baseline eGFR value (only for HbA_{1c}, FPG) as covariates.

[b] Pairwise comparison: CI based on normal approximation with continuity correction and P values based on logistic regression with terms for treatment, AHA washout, and Atherosclerotic CV Disease History and adjusting for the baseline HbA_{1c} and baseline eGFR as covariates.

[c] P value is considered nominal based on hierarchical testing sequence.

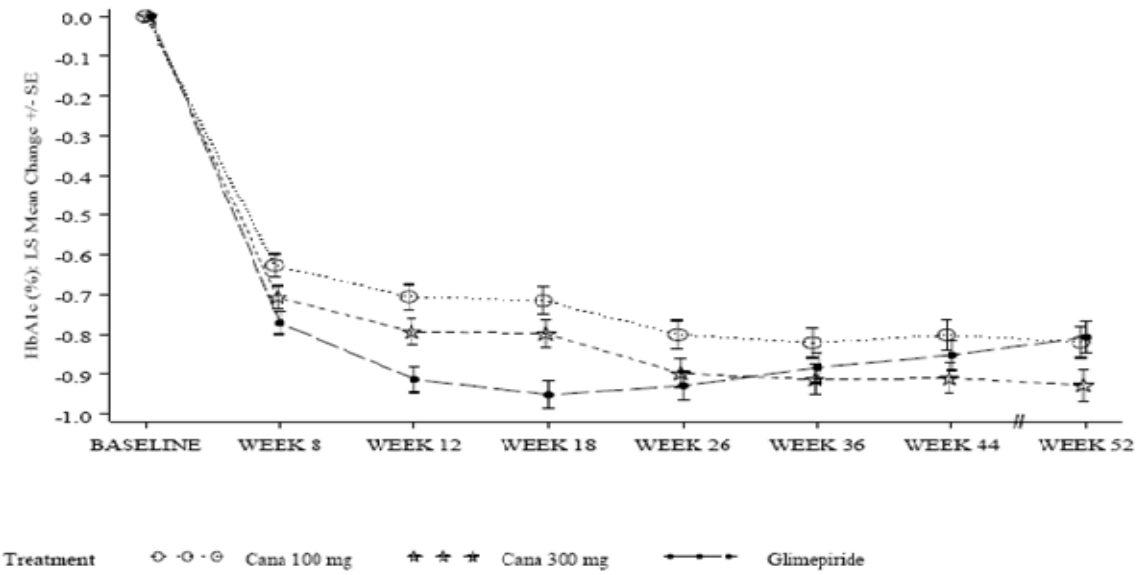
Note: LOCF; mITT analysis set

Cross-reference: ISE Tables 15 and 26

Active-Controlled Studies

In the active (glimepiride)-controlled add-on to metformin study (DIA3009), changes from baseline in HbA_{1c} mean value of 7.8% to Week 52 were -0.82% and -0.93% and for the canagliflozin 100 mg and 300 mg groups, respectively, and -0.81% for the glimepiride group (Figure 9); the upper bound of the 95% CI for the difference in HbA_{1c} for each canagliflozin group compared with glimepiride was less than the prespecified noninferiority margin of 0.3%, confirming the study's primary (for 300 mg) and key secondary (for 100 mg) noninferiority hypotheses. In addition, the upper bound of the 95% CI for the canagliflozin 300 mg group relative to glimepiride was <0, demonstrating statistical superiority of this dose of canagliflozin to glimepiride.

Figure 9: HbA_{1c}: LS Mean Change From Baseline Over Time in Active-comparator (Glimepiride) Controlled Add-on to Metformin Study (DIA3009)



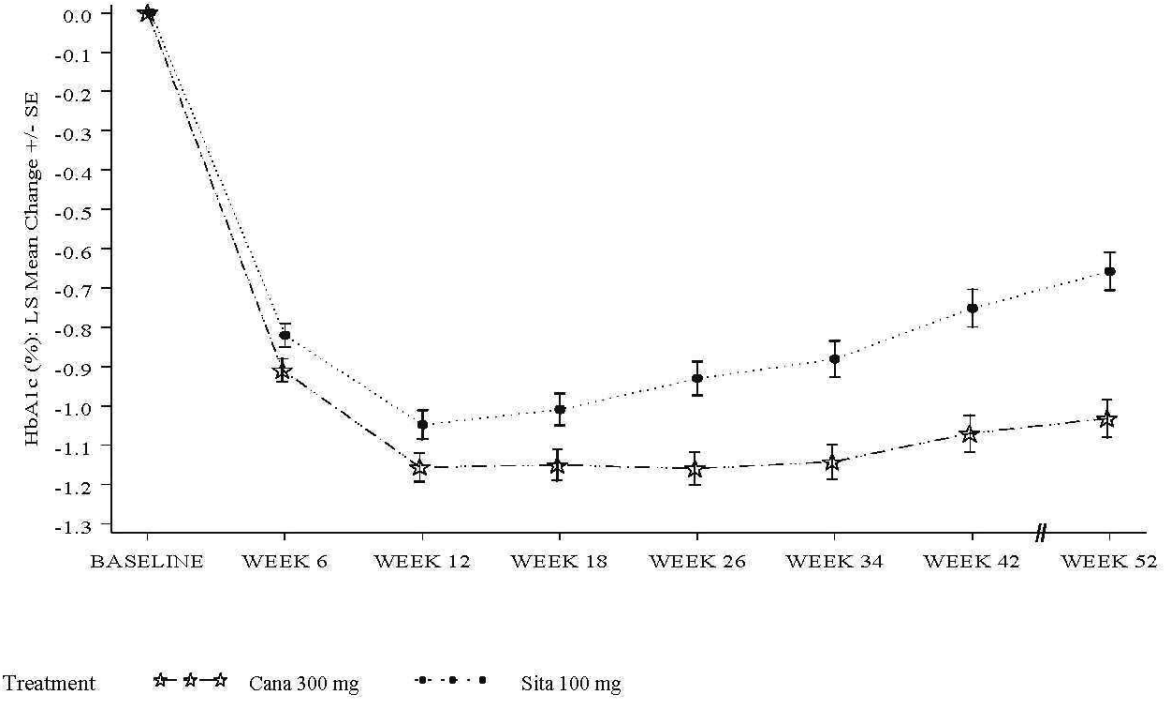
Note: CANA 100 mg (N=483), CANA 300 mg (N=485), Glimepiride (N=482)
Note: LOCF; mITT Analysis Set

In the active (sitagliptin)-controlled add-on to metformin/SU study (DIA3015), the change from baseline in HbA_{1c} mean value of 8.1% to Week 52 was -1.03% for the canagliflozin 300 mg group and -0.66% for the sitagliptin group (Figure 10). The upper bound of the 95% CI around the between-group difference with sitagliptin was <0.3% confirming non-inferiority. In addition, the upper bound of the 95% CI for canagliflozin relative to sitagliptin was <0, confirming statistical superiority of this canagliflozin 300 mg group to the sitagliptin group.

The proportion of subjects who achieved glycemic goals (HbA_{1c} <7%) was numerically larger in the canagliflozin 300 mg group and similar in the canagliflozin 100 mg relative to the glimepiride group in the DIA3009 study (53.6% and 60.1% for the canagliflozin 100 mg and 300 mg groups, respectively, and 55.8% for the glimepiride group); the proportion was also numerically larger with canagliflozin 300 mg relative to the sitagliptin group in the DIA3015 study (47.6% for the canagliflozin 300 mg group, and 35.3% for the sitagliptin group).

The LS mean reductions in FPG with canagliflozin were numerically greater than those observed with glimepiride in DIA3009 study (-24.3 mg/dL and -27.5 mg/dL for the canagliflozin 100 mg and 300 mg groups, respectively, and -18.3 mg/dL for the glimepiride group), and with sitagliptin in DIA3015 study (-29.9 mg/dL for the canagliflozin 300 mg group, and -5.9 mg/dL for the sitagliptin group). In the canagliflozin group, there was a sustained reduction in FPG over 52 weeks, with an attenuation of the FPG-lowering response seen in the sitagliptin group.

Figure 10: HbA_{1c}: LS Mean Change From Baseline Over Time in Active-comparator (Sitagliptin) Controlled Add-on to Metformin/Sulphonylurea Study (DIA3015)

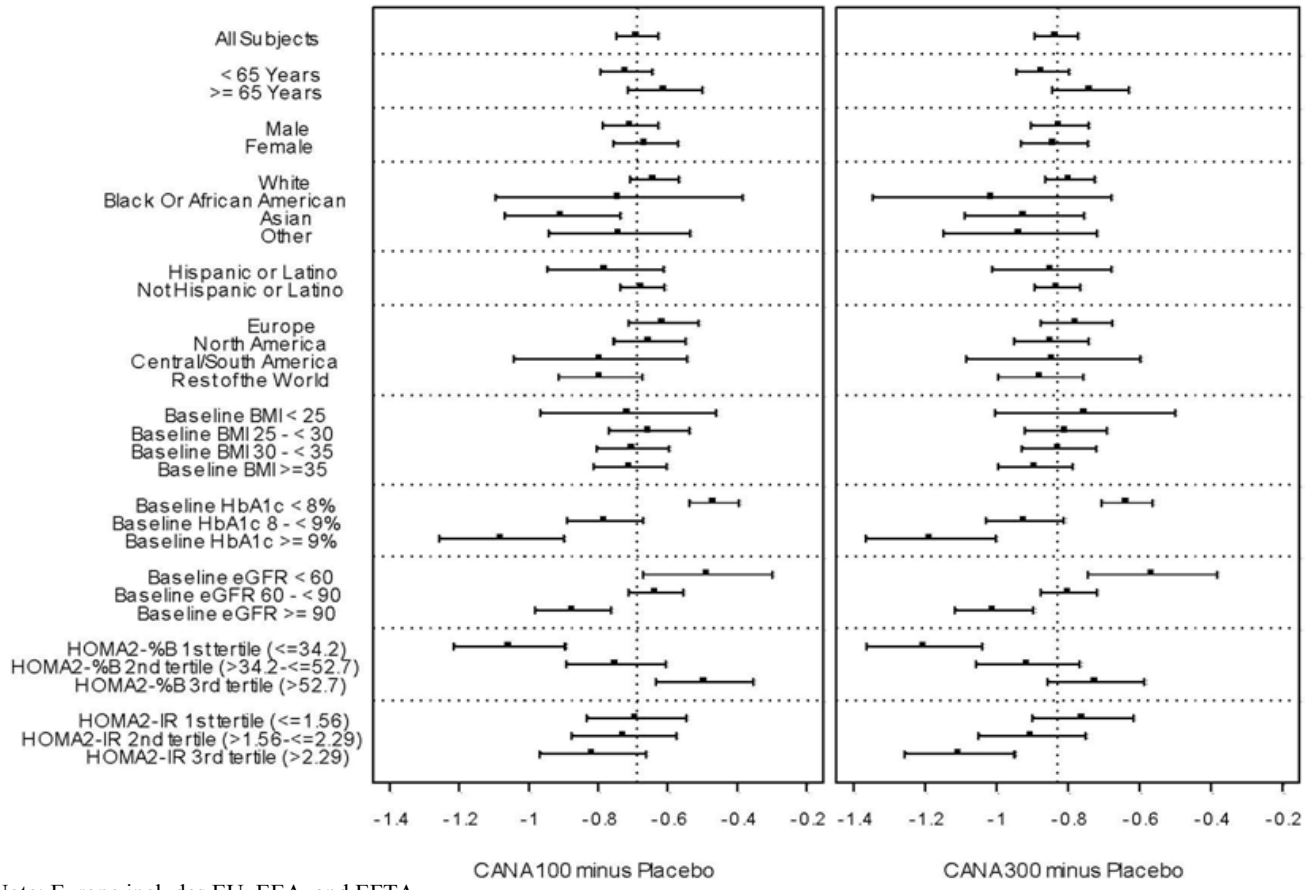


Note: CANA 300 mg (N=377), Sitagliptin (N=378)
Note: LOCF; mITT analysis set

5.3.2. Subgroup Analyses: Baseline Factors Impacting HbA_{1c} Response

Results of the subgroup analyses for the pooled population of placebo-controlled studies (see Section 5.2.2 for description) showed that treatment with canagliflozin resulted in dose-related reductions in HbA_{1c} that were consistently larger than those observed in the placebo group regardless of the subjects' demographic characteristics (age, sex, race, ethnicity), baseline BMI, baseline disease severity (ie, severity of hyperglycemia), degree of underlying renal impairment (by eGFR), or geographic region (Figure 11). The only significant treatment-by-subgroup interactions seen were for homeostatic model assessment (HOMA) measures, eGFR, and HbA_{1c}. Although the subgroups analysis by HOMA-IR and HOMA2-%B tertiles demonstrated substantial differences in HbA_{1c}-lowering, marked differences in baseline HbA_{1c} in each tertile for both factors confounded interpretation of these results. For HbA_{1c} and eGFR, stepwise larger reductions from baseline relative to placebo were seen going from lower to higher baseline HbA_{1c} categories, as well as going from lower to higher baseline eGFR categories.

Figure 11: HbA_{1c} (%) by Subgroup: Placebo-subtracted LS Mean Change (95% CI) From Baseline at Primary Assessment Time Point: Pooled Phase 3 Placebo-controlled Studies



Note: Europe includes EU, EEA, and EFTA
Note: Pairwise comparison: CIs are based on the ANCOVA model with factor(s) treatment, study and baseline HbA_{1c}.
Note: mITT analysis set
Cross-reference: attachment 1.2, FEFF03_PC.

5.3.3. Beta-Cell Function Assessments

Type 2 diabetes mellitus is characterized by increasing insulin resistance and the progressive loss of beta-cell function and insulin secretory capacity (Festa 2006, UKPDS 1995).

Beta-cell function was assessed using both fasting and dynamic (post-meal challenge) indices. In Phase 1 studies, reductions in insulin concentrations were seen with minimal changes in C-peptide concentrations—potentially reflecting greater hepatic insulin clearance. Based upon this effect of canagliflozin on insulin concentrations (that may not reflect only differences in insulin secretion), for HOMA assessments (HOMA2-%B), C-peptide rather than insulin concentrations were used.

HOMA2-%B was assessed in 6 of the canagliflozin Phase 3 studies (DIA3002, DIA3005, DIA3006, DIA3009, DIA3012, and DIA3015). In addition, in 2 placebo-controlled studies (DIA3002 and DIA3005), and in an active-controlled study (DIA3015), subjects underwent a frequently-sampled mixed meal tolerance test (FS-MMTT), supporting dynamic assessments of

beta-cell function, including a model-based analysis of the relationship between insulin secretion (based upon C-peptide deconvolution) and plasma glucose.

5.3.3.1. Assessment of Fasting Insulin Secretion Using HOMA2-%B

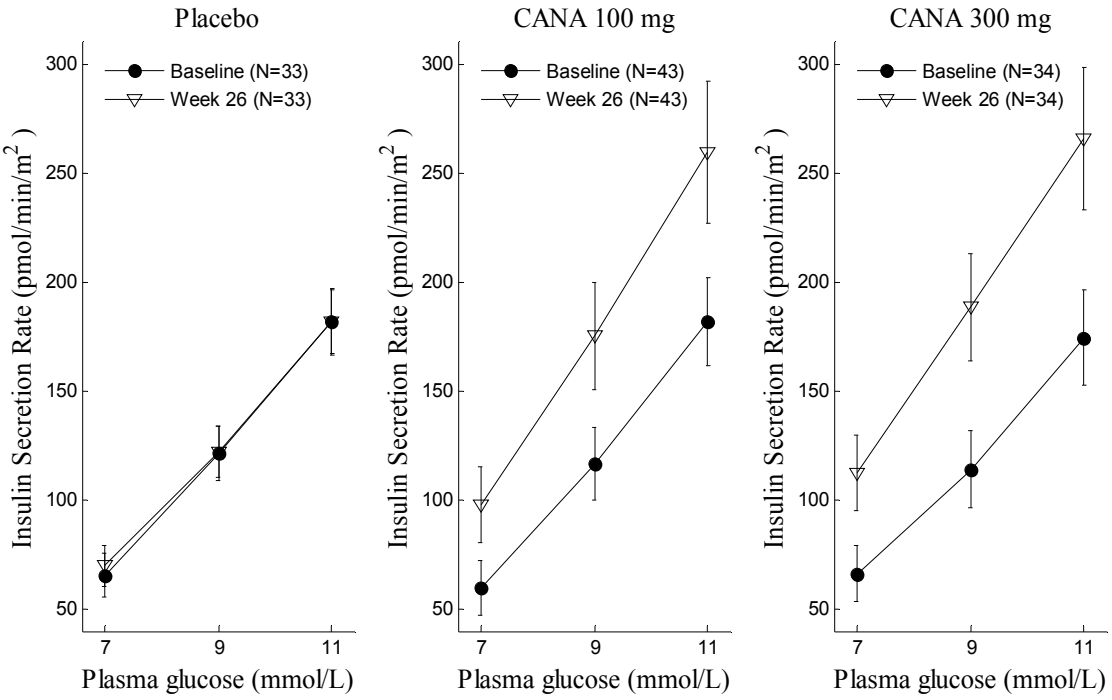
Across studies, mean improvements from baseline in HOMA2-%B were observed with canagliflozin that were larger than those observed with placebo. The placebo-subtracted LS mean increases in HOMA2-%B were modestly greater with the 300 mg dose (approximately 14% to 27%) compared to the 100 mg dose (approximately 11% to 14%) in each study. These increases in HOMA2-%B demonstrate an improvement in insulin secretion in the overnight-fasted state with canagliflozin treatment.

5.3.3.2. Beta-Cell Function During the FS-MMTT

As noted above, a subset of subjects in DIA3002, DIA3005 (Main Study), and DIA3015 underwent a FS-MMTT procedure at baseline and again at the primary assessment time point, with collection of plasma samples for measurement of glucose, insulin, and C-peptide prior to the start of the meal and at 30, 60, 90, 120, and 180 minutes after the start of the meal. Beta-cell responses were assessed based upon the relationship between the insulin secretion rate and plasma glucose concentrations (Mari 2002).

As shown in Figure 12, in study DIA3002 (add-on to metformin and SU), treatment with canagliflozin produced an upward shift in the insulin secretion rate versus plasma glucose relationship, reflecting an increased insulin secretion rate across plasma glucose concentrations. Results from the study DIA3005 (in monotherapy) were similar. For the placebo group of DIA3005 and DIA3002, there was no apparent difference or a modest decrease in the relationship between the insulin secretion rate and glucose concentrations between baseline and Week 26. As seen in Figure 12, canagliflozin treatment increased both the height and slope of the relationship line (with the slope of the relationship referred to as the glucose-sensitivity of the beta-cell). Thus at any given glucose concentration, improved responsiveness of the beta-cell is seen with canagliflozin treatment, with enhanced insulin secretion. In DIA3015, canagliflozin 300 mg and sitagliptin 100 mg treatment both provided similar improvements in this insulin secretion rate/plasma glucose relationship. It is notable that canagliflozin, which does not directly modulate the beta cell (SGLT2 is expressed only in the kidney, and not on beta-cells), produced a similar improvement in beta-cell function to that seen with sitagliptin, an agent which has as its primary mechanism of action to enhance insulin secretion (via increasing incretin levels).

Figure 12: Relationship Between Insulin Secretion Rate and Plasma Glucose Concentrations at Baseline and Week 26 (Study DIA3002: Modified Intent-to-Treat Analysis Set)



5.4. Changes in Body Weight and Composition

5.4.1. Percent Change From Baseline in Body Weight

Placebo-controlled Studies (other than the DIA3004 Renal Impairment Study)

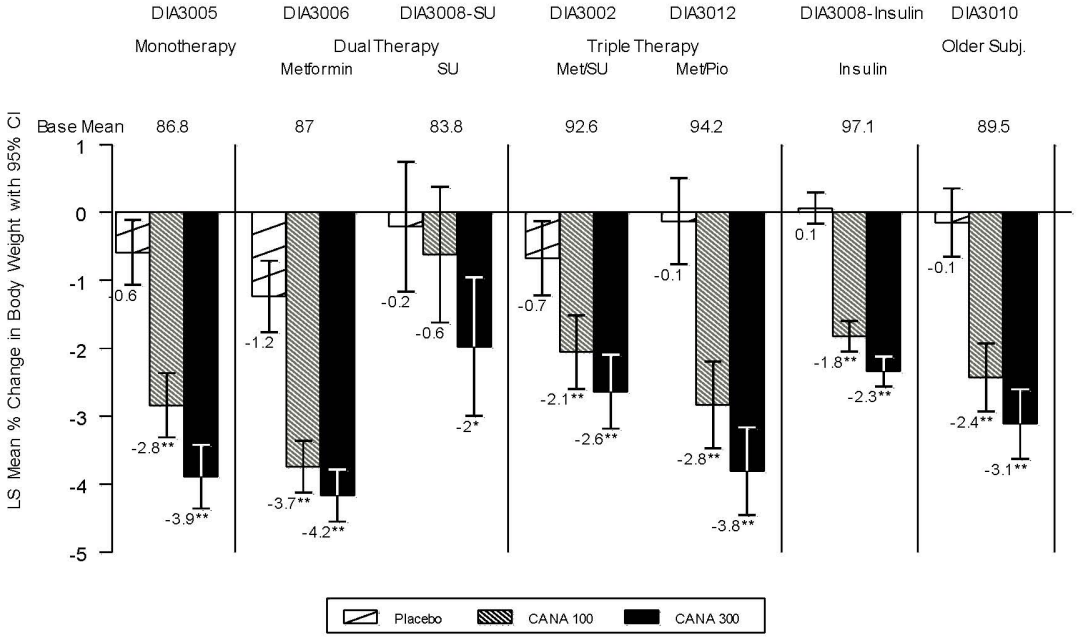
Across the placebo-controlled Phase 3 studies, the placebo-subtracted LS mean percent changes from baseline in body weight (at time of primary efficacy assessment) ranged from approximately -1.4% to -2.7% with the canagliflozin 100 mg group and from approximately -1.8% to -3.7% with the canagliflozin 300 mg group (Figure 13). Change from baseline in body weight in the high glycemic cohort of DIA3005 (monotherapy study) was similar to that observed in the main study population.

In the DIA3008 SU substudy, statistically significant weight loss was observed with the canagliflozin 300 mg group, with the magnitude of the LS mean percent change at Week 18 (-1.8%) consistent with that seen in other Phase 3 studies for the 300 mg dose. No significant reduction in body weight was seen with the canagliflozin 100 mg dose in the SU substudy (-0.4% relative to placebo).

Across Phase 3 studies, a larger body weight reduction was seen with canagliflozin 300 mg relative to canagliflozin 100 mg group, with observed incremental differences in the placebo-subtracted HbA_{1c} reduction from baseline of approximately 1.1% in the monotherapy study and ranging from 0.5% to 1.2% in the add-on combination use studies or add-on to current therapy studies (Figure 14).

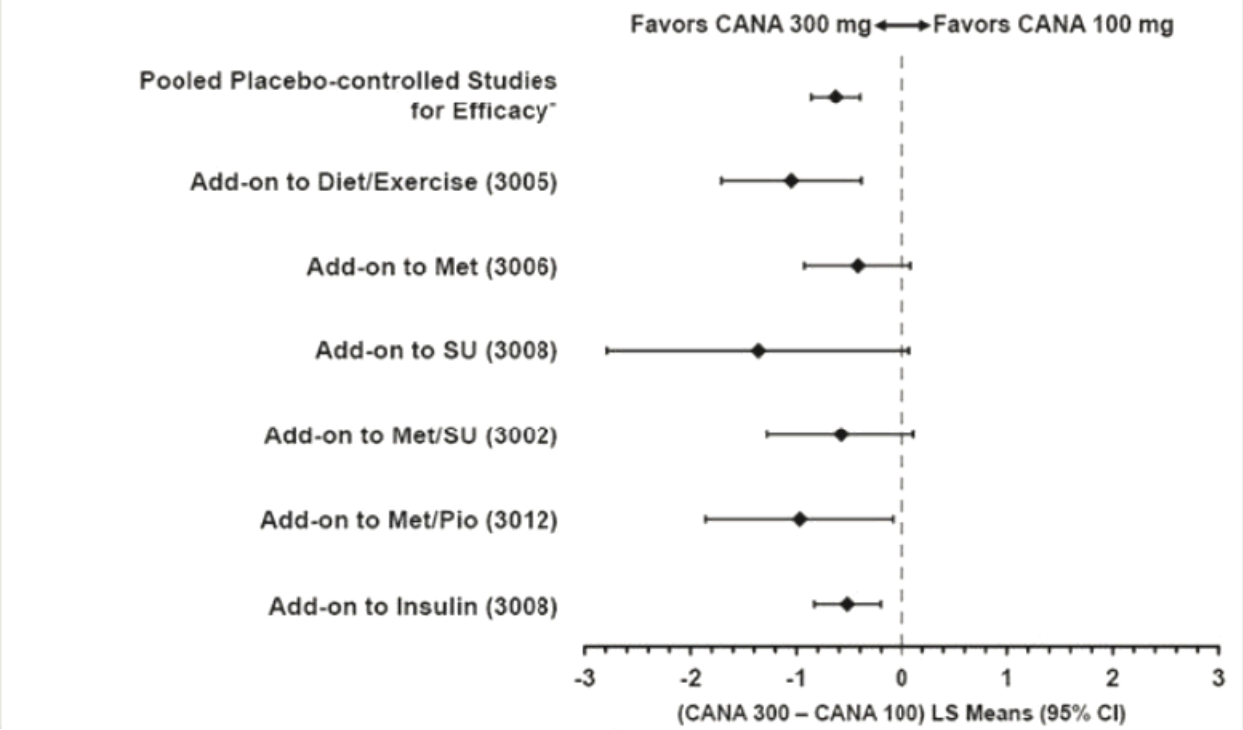
The pattern of weight loss with canagliflozin was generally consistent across studies, with a reduction seen by Week 12, and with continued weight loss at a slower rate that either continued over the 26-week treatment period or appeared to plateau at Week 18. As shown below with results from the 52 week active-comparator controlled studies, the weight loss observed at Week 26 was maintained over the longer treatment periods.

Figure 13: Body Weight: LS Mean Percent Changes From Baseline at Primary Assessment Time Point: Study-by-Study Comparison of Pooled Placebo-controlled Phase 3 Studies



** Statistically significant ($p<0.001$) [(*$p<0.05$)] vs placebo based on the ANCOVA models from individual studies.
Note: LOCF; mITT analysis set

Figure 14: Pairwise Comparison (CANA 300 mg vs CANA 100 mg) LS Means Percent Change from Baseline in Body Weight



* Includes monotherapy, dual therapy, triple therapy, and insulin add-on studies
Based on ANCOVA models, data prior to rescue (LOCF)

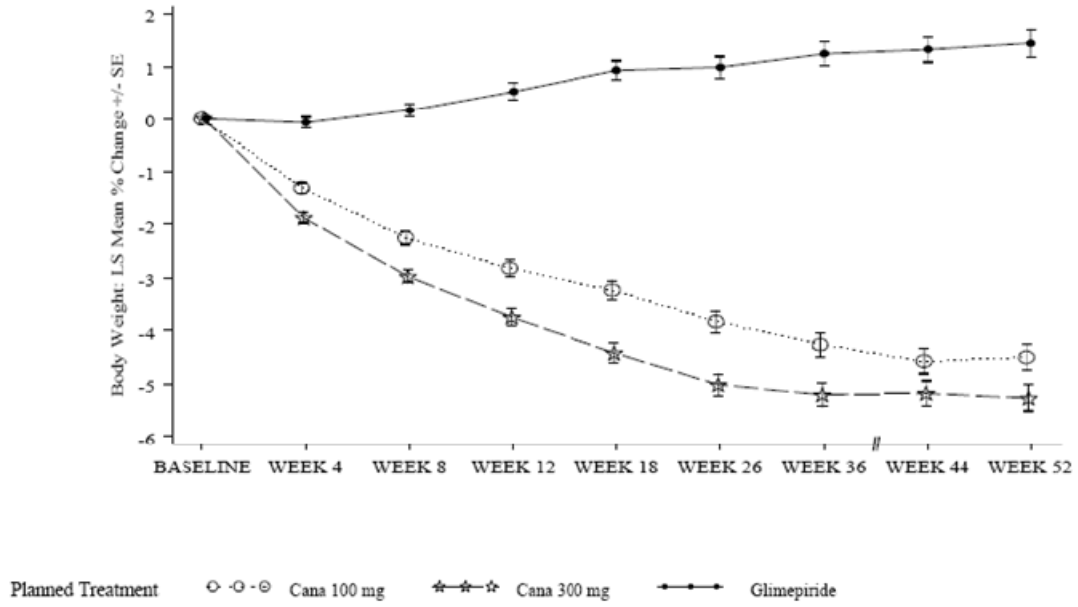
Placebo-controlled Study in Subjects with Reduced eGFR (DIA3004)

In DIA3004, the study in subjects with baseline eGFR ≥30 to <50 mL/min/1.73 m^2, modestly less weight loss was observed relative to other placebo-controlled studies, with a reduction relative to placebo of –1.6% with canagliflozin 100 mg and –1.8% with canagliflozin 300 mg. The pattern differed in that the weight loss appeared nearly maximal by Week 6 and was sustained over the remainder of the 26-week treatment period.

Active-controlled Studies

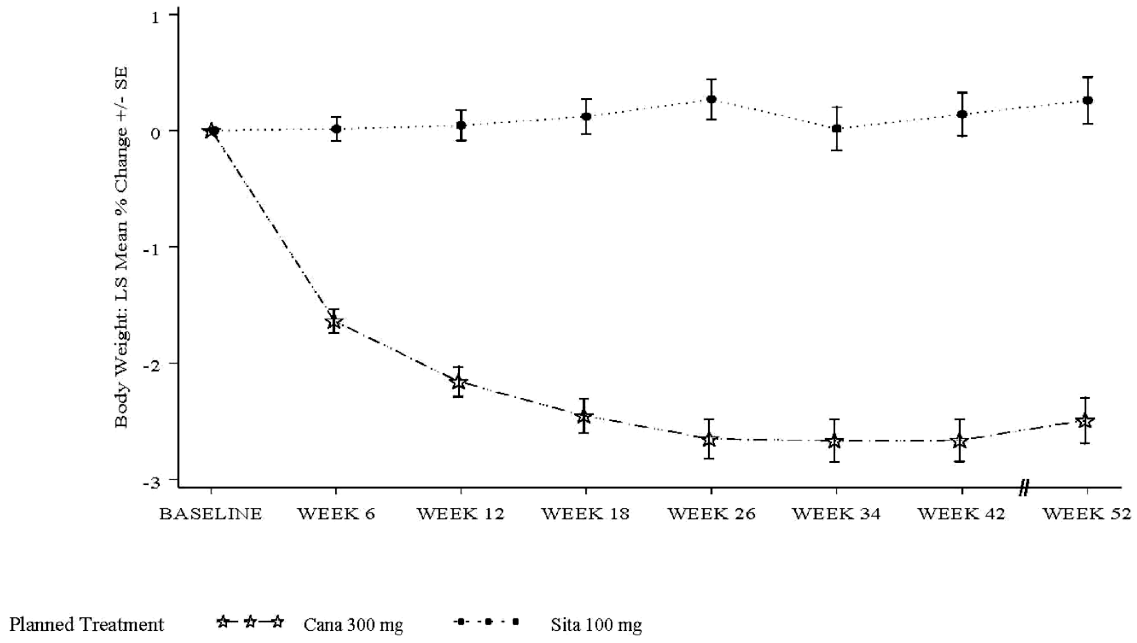
In the active-controlled comparator study (DIA3009), weight loss was seen with canagliflozin relative to weight gain with glimepiride (Figure 15); in DIA3015, weight loss was seen with canagliflozin, with a weight neutral effect of sitagliptin (Figure 16). Sustained reductions in body weight with canagliflozin were observed over the 52-week treatment periods in the DIA3009 and DIA3015 studies.

Figure 15: Body Weight: LS Mean Percent Change From Baseline Over Time in Active-comparator (Glimepiride) Controlled Add-on to Metformin Study (DIA3009)



Note: Cana 100 mg (N=483), Cana 300 mg (N=485), Glimepiride (N=482)
Note: LOCF; mITT analysis set

Figure 16: Body Weight: LS Mean Percent Change From Baseline Over Time in Active-comparator (Sitagliptin) Controlled Add-on to Metformin/Sulphonylurea Study (DIA3015)



Note: Cana 300 mg (N=377), Sitagliptin (N=378)
Note: LOCF; mITT analysis set

5.4.1.1. Subgroup Analyses: Baseline Factors Impacting Body Weight Loss Response

Results of the subgroup analyses for the pooled population of placebo-controlled studies (see Section 5.2.2 for description) showed that treatment with canagliflozin lowered body weight in a dose-related manner at the primary assessment time point, with the mean percent reductions in body weight consistently larger than those observed in the placebo group regardless of the subjects' demographic characteristics (age, sex, race, ethnicity), baseline BMI, baseline disease severity (ie, severity of hyperglycemia), or degree of underlying renal impairment. Statistically significant interactions (at an α=0.10 level) were found for subgroups defined by baseline BMI (p=0.0798), with absolute mean reductions relative to placebo increasing in a stepwise manner as baseline BMI increased, and for baseline eGFR (p=0.0432), with greater percent reductions seen in subjects with an eGFR ≥90 mL/min/1.73 m^2 compared with those subjects had an eGFR of <60 mL/min/1.73 m^2). Both of these significant interactions are considered to be quantitative in nature, as the treatment effects in all subgroups were in the same direction.

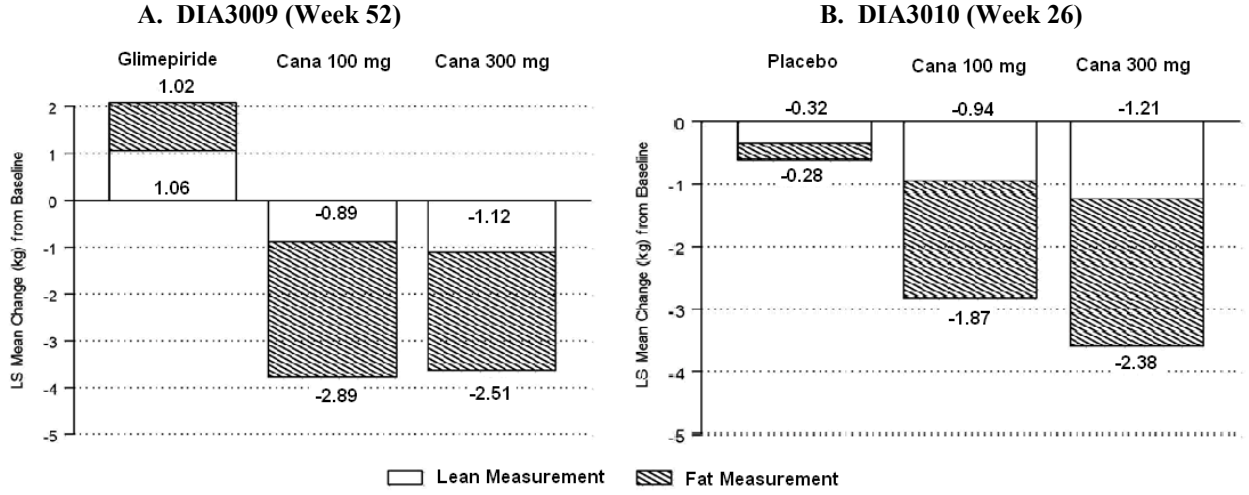
5.4.2. Changes from Baseline in Lean Body Mass and Visceral Adiposity

Two Phase 3 studies, DIA3009 (active-comparator [glimepiride] controlled add-on to metformin study) and DIA3010 (placebo-controlled study in older T2DM subjects), employed DXA to assess changes in body composition, including changes in body fat mass and lean body mass, in a subset of subjects. Study DIA3009 also included an abdominal CT scan to evaluate changes in abdominal fat distribution. In DIA3009 approximately 21% of subjects and in DIA3010 approximately 30% of subjects participated in the body composition substudies. The change from baseline in total body fat mass was a prespecified major secondary endpoint (associated with hypothesis testing) for DIA3010.

In both studies, the LS mean reductions in body weight seen with canagliflozin treatment in the body composition subgroup were similar to those observed in the overall study population. In DIA3009, the reductions relative to glimepiride in the body composition substudy (N=312) were –5.3 kg and –5.0 kg in the 100 mg and 300 mg canagliflozin groups, respectively, and –4.4 kg and –4.7 kg in the overall study population, in the 100 mg and 300 mg canagliflozin groups, respectively. In DIA3010, the reductions relative to placebo in the body composition substudy were -2.3 and -3.0 kg in the 100 mg and 300 mg canagliflozin groups, respectively, and -2.1 and -2.7 kg in the canagliflozin 100 mg and 300 mg groups, respectively, for the overall study population.

In both studies (Figure 17 A [DIA3009] and B [DIA3010]), the reduction with canagliflozin in fat mass was approximately twice as large as the reduction in lean mass, similar to results reported for other AHAs associated with weight loss (Bolinder 2012, Jendle 2009) and with restricted calorie diet-induced weight loss (Albu 2010, Brehm 2003, Redman 2007).

Figure 17: Body Composition Using DXA Analysis: Mean Change From Baseline



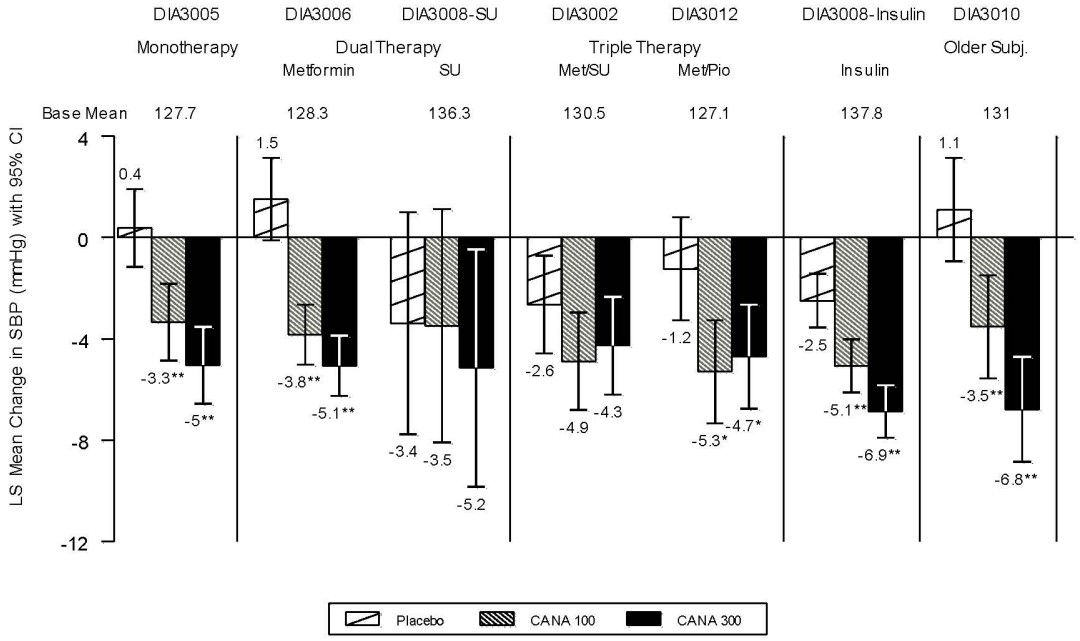
Note: the LS means are derived from the ANCOVA model with treatment, study specific stratification factors and baseline value.

In addition to the assessment of effect of canagliflozin on overall body fat changes, changes in fat distribution in visceral and subcutaneous adipose tissue mass (VAT and SAT, respectively) were also explored using an abdominal CT scan in DIA3009. For the visceral region, the true VAT (ie, VAT adjusted for organ tissue fat) was used for the analysis and compared with SAT. Results showed a slightly greater percent reduction in visceral adipose tissue relative to subcutaneous fat stores following treatment with canagliflozin, with no apparent dose response.

5.5. Blood Pressure-Lowering Effects

Across the placebo-controlled Phase 3 studies, the placebo-subtracted LS mean changes from baseline in SBP (at time of primary efficacy assessment) ranged from -2.2 to -5.7 mm Hg with the canagliflozin 100 mg group and from -1.6 to -7.9 mmHg with the canagliflozin 300 mg group (Figure 18). The reductions were observed at the first measurement (Week 6), and remained generally stable over the remainder of the treatment periods. In the DIA3005 monotherapy study High Glycemic Substudy, the LS mean reductions from baseline were similar to those observed across the Phase 3 studies, with decreases of -4.47 and -4.97 mmHg for the canagliflozin 100 mg and 300 mg groups, respectively.

Figure 18: Systolic Blood Pressure (mmHg) LS Mean Changes From Baseline at Primary Assessment Time Point: Study-by-Study Comparison of Placebo-controlled Phase 3 Studies



** Statistically significant ($p<0.001$) [(*$p<0.05$)] vs placebo based on the ANCOVA models from individual studies.
Note: LOCF; mITT analysis set

Results in the DIA3004 study, in subjects with renal impairment, were generally similar to results across the Phase 3 studies. Substantial numerical reductions from baseline in SBP were observed with both canagliflozin doses: at Week 26, the LS mean change from baseline relative to placebo was –5.73 mmHg (95% CI [-9.55, -1.91]) for canagliflozin 100 mg and –6.12 mmHg (95% CI [-9.96, -2.28]) for canagliflozin 300 mg.

Treatment with canagliflozin was associated with larger mean decreases from baseline in SBP compared to glimepiride in DIA3009 (between group differences relative to glimepiride of -3.48 and -4.76 mmHg for the 100 mg and 300 mg doses, respectively) or compared to sitagliptin in DIA3015 (between-group difference relative to sitagliptin of -5.91 mmHg for the 300 mg dose).

The reductions in SBP were sustained over the 26-week treatment periods in the placebo-controlled studies and the 52-week treatment periods in the active-controlled studies.

Reductions from baseline in diastolic blood pressure (DBP) were also observed in both canagliflozin groups in each of the Phase 3 studies, with the LS mean changes from baseline relative to placebo at the primary assessment time point across the studies ranging from -1.02 to -2.47 mmHg for the canagliflozin 100 mg group and -0.53 to -3.22 mmHg for the canagliflozin 300 mg group. The LS mean reductions were numerically larger than those for the placebo group in the placebo-controlled studies. No notable changes in pulse rate were observed across the Phase 3 studies with canagliflozin treatment.

The decreases in BP with canagliflozin relative to placebo did not appear to be meaningfully different in subgroups of subjects based upon baseline concomitant antihypertensive medication

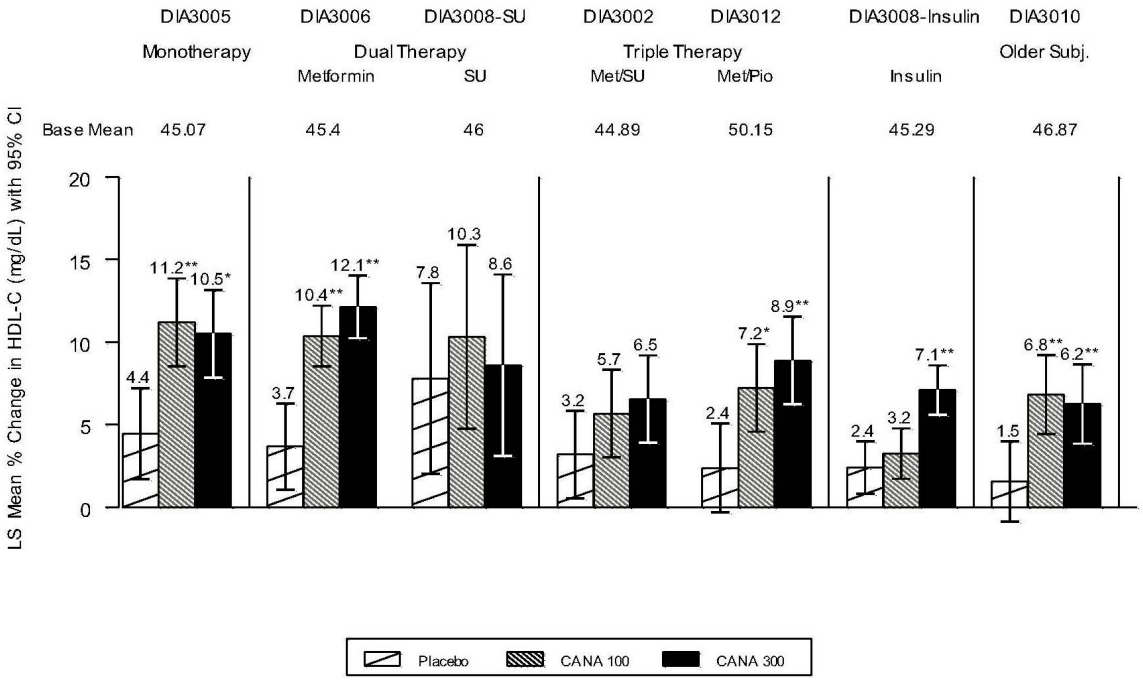
use, specifically angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), or diuretics.

5.6. Effects on Fasting Plasma Lipids

The effects of canagliflozin on low-density lipoprotein-cholesterol (LDL-C) are reviewed and discussed in Section 6.7.

Mean percent increases in HDL-C were observed in the canagliflozin 100 mg and 300 mg groups relative to placebo (ranging from 0.8 to 6.8% with the 100 mg dose and 0.9 to 8.4% with the 300 mg dose) in Phase 3 studies, and were statistically significantly greater than those observed with placebo in most studies (Figure 19). While larger LS mean percent reductions in fasting TG with the canagliflozin groups compared with placebo group were seen in most of the Phase 3 studies, the treatment difference were generally small and often not statistically significant for individual studies.

Figure 19: Least Squares Mean Percent Changes From Baseline in HDL-C (mg/dL) at Primary Assessment Time Point- LOCF: Study-by-Study Comparison for Placebo-Controlled Studies (ISE Phase 3 Studies: Modified Intent-to-Treat Analysis Set)



** Statistically significant ($p<0.001$) vs placebo based on the ANCOVA models from individual studies. Numbers in graphs represent the LS mean percent change in HDL-C.

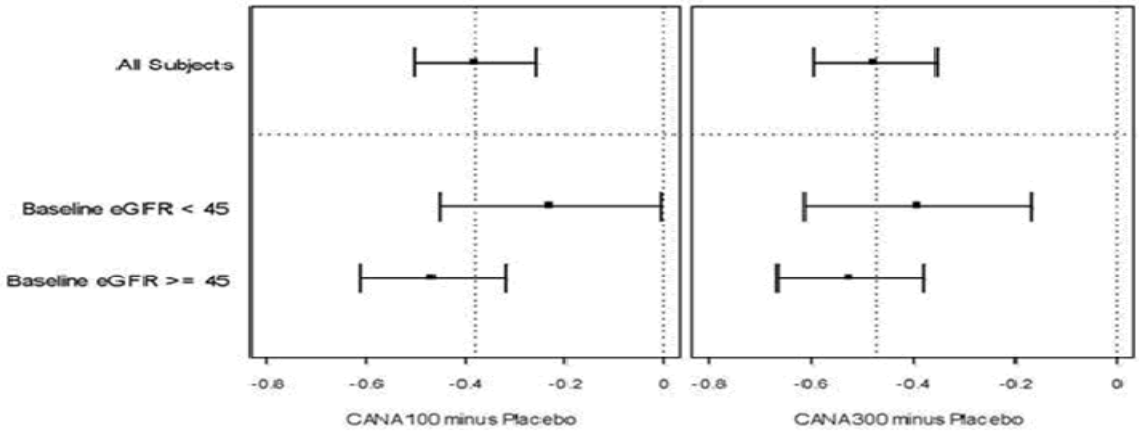
5.7. Pooled Population of Subjects with Renal Impairment (Stage 3 NKF: eGFR ≥30 to <60 mL/min/1.73 m^2)

Baseline characteristics, including baseline renal function, are described in Section 5.2.2.

The change from baseline in HbA_{1c} and the percent change from baseline in body weight to the primary assessment time point were analyzed for the overall pooled renal impairment population and for subgroups defined by baseline eGFR (<45 and ≥45 mL/min/1.73 m^2). Estimates of the LS mean differences relative to placebo and 95% CI for the changes in HbA_{1c} and percent and absolute changes in body weight were analyzed for the overall population and for each of these subgroups.

Results in this pooled population showed dose-related LS mean reductions in HbA_{1c} relative to placebo: -0.38% and -0.47% for canagliflozin 100 mg and 300 mg, respectively ($p<0.001$ for comparisons with both doses). Least squares mean changes from baseline in HbA_{1c} based on baseline eGFR categories of <45 and ≥45 mL/min/1.73 m^2 and for the overall pooled population are presented in Figure 20.

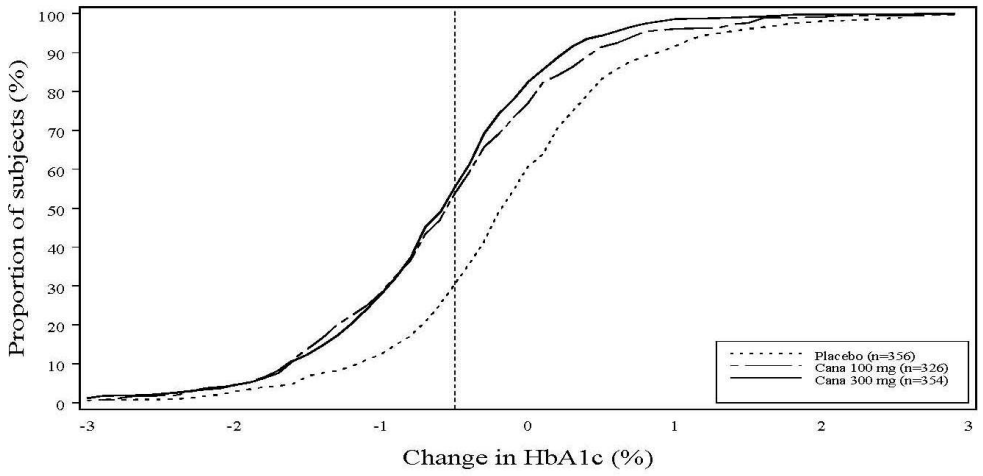
Figure 20: HbA_{1c} (%) by Baseline eGFR: Placebo-subtracted LS Mean Changes From Baseline at Primary Assessment Time Point: Pooled Phase 3 Studies in Subjects With Renal Impairment



Note: Pairwise comparison: LS means and CIs are based on the ANCOVA model with factor(s) treatment, study and baseline HbA_{1c} as a covariate. LOCF; mITT analysis set

Although the mean reductions from baseline in HbA_{1c} were smaller than observed in subjects with normal or only mildly impaired renal function, a moderate proportion of subjects in this cohort, greater than seen in the placebo group, obtained larger responses (eg, >0.5% HbA_{1c}-lowering), as is seen in the cumulative distribution plots for HbA_{1c}-lowering (Figure 21).

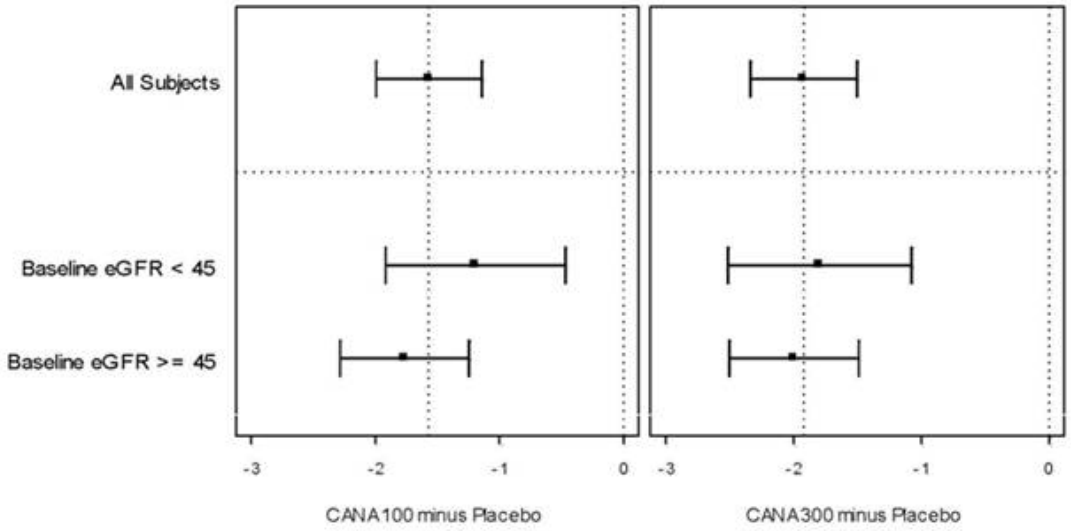
Figure 21: HbA_{1c} (%): Cumulative Distribution Plot of Change from Baseline at End Point in the Pooled Renal Population



For the canagliflozin 100 mg and 300 mg groups, placebo-subtracted LS mean absolute changes of -1.38 kg and -1.76 kg, respectively, from baseline in body weight were observed ($p<0.001$ for both comparisons), with a placebo-subtracted LS mean percent changes of -1.6% and -1.9%, respectively ($p<0.001$ for both comparisons).

Results of the analyses of the percent change in body weight to the primary assessment time point (LOCF) for baseline eGFR categories of <45 and ≥45 mL/min/1.73 m^2 and overall are shown in the Forest plot displayed in Figure 22.

Figure 22: Body Weight (kg) by Baseline eGFR: Placebo-Subtracted LS Mean Percent Changes From Baseline at Primary Assessment Time Point: Pooled Phase 3 Studies in Subjects With Renal Impairment



Note: Pairwise comparison: LS means and CIs are based on the ANCOVA model with factor(s) treatment, study and baseline body weight as a covariate. LOCF; mITT analysis set

For SBP, absolute changes in the placebo-subtracted LS means from baseline to the primary assessment time point (LOCF) were observed in the canagliflozin 100 mg group (-2.77 mmHg [p=0.0059]) and canagliflozin 300 mg group (-4.38 mmHg [p<0.001]). In the subpopulation of subjects with eGFR 30 to <45 mL/min/1.73 m^2, and 45 to <60 mL/min/1.73 m^2, the placebo-subtracted LS means of SBP reduction from baseline to the primary assessment time point (LOCF) in the canagliflozin 100 mg group were -4.84 mmHg and -1.82, mmHg, respectively, and in canagliflozin 300 mg group -4.88 mmHg and -4.25 mmHg, respectively.

6. CLINICAL SAFETY

6.1. Overview

The safety of canagliflozin was evaluated in 10,285 subjects with T2DM (who received at least 1 dose of double-blind study drug), including 3,092 subjects treated with canagliflozin 100 mg and 3,462 subjects treated with canagliflozin 300 mg, enrolled in 9 double-blind, controlled Phase 3 clinical studies.

Potential safety or tolerability issues identified during either preclinical development, early clinical development, or in published reports from the clinical development of other SGLT2 inhibitors were studied in greater detail throughout the program and included urinary tract infections (UTI), genital infections, photosensitivity, venous thromboembolism, and bone safety. Detailed evaluations of renal safety, hepatic safety, and CV events (for MACE-plus) were also

conducted, including adjudication of potentially clinically significant events (based upon pre-specified criteria). Based upon clinical observations from Phase 3 results, additional analyses of adverse events related to the osmotic diuresis associated with canagliflozin (eg, thirst or pollakiuria) or associated with reduced intravascular volume (eg, postural dizziness) were also conducted.

Safety evaluations included collection of adverse events, safety laboratory tests (including chemistry, hematology, and urinalysis), 12-lead ECG, vital signs (BP, heart rate), body weight, physical examinations, and review of hypoglycemic episodes.

6.1.1. Populations Supporting Safety

In addition to a review of safety results by individual studies (see Table 4 for overview of individual studies) which focus on the safety and tolerability profile in clinical settings defined by specific use (eg, monotherapy or add-on use to specific AHA combinations), or in special safety studies conducted in specific populations (ie, study in subjects with renal impairment, study in older subjects; or study in subjects with or at high risk for CV disease), 3 pre-specified pooled datasets from the Phase 3 studies were constructed to address specific safety objectives. These pooled safety datasets provide the broadest and most robust safety assessments and, therefore, are the primary focus of safety data in this Briefing Document.

Detailed information on the construction of each of these pooled datasets is presented in Table 6. Information from specific studies is also presented, where relevant.

An important pooled population for assessment of safety was the Phase 3 **Placebo-controlled Studies Dataset**, which included 4 Phase 3 studies with a similar design, a broad range of subjects, not specifically selected by particular subject characteristics (other than background diabetes treatment regimen). Therefore, the Placebo-controlled Studies Dataset provided a broad and general T2DM experience, over a common duration of treatment, and with a placebo-control supporting a detailed and robust assessment of safety and tolerability. For these reasons, this population was used as the initial source for determination of adverse drug reactions (ADRs), as discussed in Section 6.3.1.

The largest pooled population included subjects from 8 of the 9 Phase 3 studies (all studies that examined both doses of canagliflozin) referred to as the **Broad Dataset** and was intended to support and extend assessments performed in the Placebo-controlled Studies Dataset, in particular, the detection of lower incident adverse events. Fifty-six percent of this Broad Dataset comes from studies conducted in selected populations (study in older subjects [DIA3010], the study in subjects with renal impairment [DIA3004], and the study in subjects with or at high risk of CV disease [DIA3008]). Relative to the Placebo-controlled Studies Dataset, these latter 3 studies generally included older subjects with a longer duration of diabetes, a higher baseline prevalence of diabetic comorbidities and complications, and a higher proportion of subjects on insulin treatment. To provide groups with comparable exposure across canagliflozin and controls, given substantial differences in exposure within individual studies, a single comparator group, pooling subjects in placebo and active comparator (glimepiride, sitagliptin) treatment

groups, was created. Thus, in this dataset the pooled groups included canagliflozin 100 mg, canagliflozin 300 mg, combined canagliflozin groups, and the "non-canagliflozin" (non-CANA) control group.

An additional dataset (referred to as the **Pooled Renal Impairment Dataset**) was constructed to expand the experience in subjects with Stage 3 renal impairment (eGFR values ≥30 and <60 mL/min/1.73 m^2; NKF KDOQI Guidelines 2000).

Note that for the largest pooled dataset (referred to as the Broad Dataset), 3 sequential analyses were conducted, 2 included in the NDA, and the latest with a cut-off date of 1 July 2012 that was included in the 4-month safety update report. These analyses are also summarized in Table 6.

Since the Broad Dataset was the largest dataset, and included a broader range of subjects, including more vulnerable subjects, as discussed above, results from this dataset are the focus in this Briefing Document (using results providing the longest exposure [results to 01 July 2012]), with other dataset results presented where appropriate.

The safety data presented in this document is primarily focused on the analysis of all data, regardless of initiation of rescue therapy (ie, new agent or increased dose of antihyperglycemic therapy, as defined as rescue therapy in each protocol) so as to provide the most comprehensive approach to the safety analyses. In contrast, hypoglycemia is assessed based on the data cut-off prior to the addition of rescue therapy (which in some studies included use of a sulphonylurea or insulin).

Table 6: Pooled Safety Assessment Datasets for Phase 3 Studies

Dataset Name	Dataset Description	Studies Pooled	Objectives	Pooled Treatment Groups	Duration
Placebo-controlled Studies Dataset	Includes the 26-week placebo-controlled Phase 3 studies	DIA3002, DIA3005,[a] DIA3006,[b] DIA3012	Evaluate the safety and tolerability of canagliflozin based upon a large subject sample by pooling placebo-controlled Phase 3 studies of generally similar design	Placebo Canagliflozin 100 mg Canagliflozin 300 mg All Canagliflozin	26 weeks
Pooled Renal Impairment Dataset[c]	Subjects with baseline eGFR ≥30 to <60 mL/min/1.73 m^2	DIA3004 and subgroups from DIA3005, DIA3008, DIA3010	Evaluate safety and tolerability within a special population of subjects with renal insufficiency with eGFR ≥30 to <60 mL/min/1.73 m^2	Placebo Canagliflozin 100 mg Canagliflozin 300 mg All Canagliflozin	26 weeks/ Through date cutoff for DIA3008[d]
Broad Dataset Core	All Active- and Placebo-controlled studies examining both canagliflozin doses[e]	DIA3002, DIA3004, DIA3005,[a] DIA3006, DIA3008, DIA3009, DIA3010, DIA3012	Large pooled dataset from controlled clinical studies (active and placebo-controlled) to identify less common safety signals, and to support safety assessments in the Placebo-controlled Studies Dataset in the NDA.	Canagliflozin 100 mg Canagliflozin 300 mg All Canagliflozin All Non-Canagliflozin (placebo, sitagliptin or glimepiride)	26 weeks for all studies other than DIA3009 and DIA3008; 52 weeks for DIA3009; Through date cutoff for DIA3008[d]
Broad Dataset – 31 January 2012			Longer-term exposure dataset to evaluate selected adverse events occurring with low incidence (eg, skin photosensitivity, specific malignancies) and events undergoing adjudication (including CV events) for the NDA.		Data collected through 31 January 2012
Broad Dataset- 01 July 2012			Longer term exposure dataset for the 4 month safety update report		Data collected through 01 July 2012

[a] DIA3005: Excluding the high glycemic substudy
[b] DIA3006: Excluding sitagliptin treatment group
[c] Subjects with renal impairment will be included defined as with a baseline eGFR of ≥30 to <60 mL/min/1.73 m^2 consistent with National Kidney Foundation (Stage 3) and the FDA guidance. Subjects included in this population will come from studies DIA3004, DIA3005, DIA3008 and DIA3010. The applicable eGFR ranges at screening for each study are as follows: DIA3004: ≥30 to <50 mL/min/1.73 m^2; DIA3005: ≥50 to <60 mL/min/1.73 m^2; DIA3008: ≥30 to <60 mL/min/1.73 m^2; DIA3010: ≥50 to <60 mL/min/1.73 m^2
[d] DIA3008 date cutoff is 15 September 2011
[e] Excluding DIA3015 study

6.1.2. Baseline Characteristics and Extent of Exposure

Placebo-controlled Studies Dataset

Baseline demographic and anthropometric characteristics were generally similar across treatment groups (Attachment 6). The median age of subjects was 57 years. The proportion of men and women was approximately equal. With regard to ethnic/racial backgrounds, 72% of the subjects were white, 12% of subjects were Asian, and 5% of subjects were black or African-American. Approximately one-quarter (26%) of subjects were of Hispanic or Latino ethnicity. The mean BMI was 32.1 kg/m^2 and more than half of the subjects (58%) were obese (BMI ≥30 kg/m^2).

The mean duration of exposure to study drug for the 26-week double-blind treatment period was 24 weeks in the combined canagliflozin group, about 0.5 weeks longer than in the placebo group. The proportion of subjects having at least 24 weeks of exposure was 87.6% in the combined canagliflozin group compared with 83.1% in the placebo group (Attachment 7).

Broad Dataset

Baseline demographic characteristics were generally similar across treatment groups (Attachment 8). The median age of subjects was 60 years, with a higher proportion of males compared with females. Whites represented the most common racial group in all studies (72.6%). However, there was substantial representation of Asian subjects, with a smaller representation of black or African-American subjects. Of the 359 black or African American subjects included in this dataset, the majority (313 subjects) were recruited from the United States (US) and represent 13.3% of the 2,355 subjects randomized from the US (in study DIA3015, which is not included in the Broad dataset, and additional 88 black or African American subjects were randomized). Nearly 16% of subjects were of Hispanic/Latino ethnicity.

With regard to anthropometric baseline characteristics, across treatment groups, a high proportion of subjects were overweight (WHO 1997) or obese, with a mean baseline BMI of 31.9 kg/m^2. Given the wide range of studies included in this dataset, subjects in the Broad Dataset included those with relatively early-onset disease and a low prevalence of diabetic complications (eg, from monotherapy study [DIA3005]) as well as those with long-standing disease with a high prevalence of diabetic complications and comorbid conditions such as diabetic nephropathy, hypertension, dyslipidemia, and pre-existing CV disease (eg, from the renal impairment study [DIA3004] and from the study in subjects with or at high risk for CV disease [DIA3008]).

In the analysis of this dataset through 01 July 2012, the mean duration of exposure to study drug was 68 weeks in the combined canagliflozin group compared with 64 weeks in the non-canagliflozin group (Attachment 9). The proportion of subjects with at least 50 weeks and at least 76 weeks of exposure was 83% and 46%, respectively, in the combined canagliflozin group, and 78% and 41%, respectively, in the non-canagliflozin group. The total exposure to canagliflozin in the analysis to 01 July 2012 was 8,063 subject-years.

Pooled Renal Impairment Dataset

Baseline demographic and anthropometric characteristics were generally similar across treatment groups (Attachment 10). The median age of subjects was 67 years. Men comprised 58% of the subjects. With regard to racial/ethnic background, 78% of the subjects were white, 13% of subjects were Asian, and 3% of subjects were black or African-American. Overall, 9% of subjects were of Hispanic or Latino ethnicity. The mean BMI was 32.5 kg/m^2 and more than half of the subjects (64%) were obese (BMI ≥30 kg/m^2).

Mean eGFR in this population was 48.2 mL/min/1.73 m^2 and similar across treatment groups (47.8 to 48.8 mL/min/1.73 m^2). Median eGFR was 50.0 mL/min/1.73 m^2 (49.1 to 51.0 mL/min/1.73 m^2) with about one third of the subjects with baseline eGFR 30 to <45 mL/min/1.73 m^2.

The mean duration of exposure (up to 01 July 2012) to study drug was 37 weeks in the combined canagliflozin group compared with 36 weeks in the placebo group (Attachment 11). The majority of subjects had an exposure to study drug that ranged from 24 weeks to 76 weeks.

6.1.3. Disposition

To provide an overall experience with regard to subject disposition with reasons for withdrawal, results from the Broad Dataset (results to 01 July 2012) are presented in this section. Reasons for withdrawal were generally similar across the pooled datasets.

Overall, 24.4% of subjects withdrew from the studies (mean duration of exposure of 68 weeks in the canagliflozin groups and 64 weeks in the non-canagliflozin group), with a numerically higher proportion in the non-canagliflozin group (28.3%) withdrawing compared with the combined canagliflozin group (22.3%) (Table 7).

Table 7: Subject Disposition in Broad Dataset (through 01 July 2012)

	All Non-CANA (N=3270) n (%)	CANA 100 mg (N=3095) n (%)	CANA 300 mg (N=3089) n (%)	All CANA (N=6184) n (%)	Total (N=9454) n (%)
Subjects randomized	3270 (100)	3095 (100)	3089 (100)	6184 (100)	9454 (100)
Subjects randomized, but not dosed	8 (0.2)	3 (0.1)	4 (0.1)	7 (0.1)	15 (0.2)
Subjects in the safety analysis set	3262 (99.8)	3092 (99.9)	3085 (99.9)	6177 (99.9)	9439 (99.8)
Subjects who received rescue therapy	573 (17.5)	305 (9.9)	201 (6.5)	506 (8.2)	1079 (11.4)
Subjects who withdrew from the study	925 (28.3)	686 (22.2)	695 (22.5)	1381 (22.3)	2306 (24.4)
Subjects completed or continuing	2337 (71.5)	2406 (77.7)	2390 (77.4)	4796 (77.6)	7133 (75.4)

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: 4-Month Safety Update (4MSU) Table 3; tsub010401jul12rds04.rtf generated by rds04.sas, 07SEP2012 12:04

A summary of reasons for withdrawal is provided in Attachment 12. The 2 most common specific reasons for discontinuation were adverse event (5.8% of total subjects) and 'other' (5.7% of total subjects). 'Other' included a variety of reasons (eg, personal reasons, moving, family-, job- or schedule-related, lack of efficacy [and not on rescue therapy], disallowed therapy, treatment unblinded, transportation challenges, site closure). Other specific reasons for

discontinuation were uncommon, with any specific reason occurring in ≤4% of the total randomized subjects. Adverse events that led to discontinuation are discussed in Section 6.2.3. In general, only small differences across treatment groups for specific reasons for discontinuation were observed. It should be noted that the mean exposure was greater in the combined canagliflozin group relative to the non-canagliflozin group (with an even larger difference in median exposure) which may contribute to modest imbalances observed (Section 6.1.2).

6.2. Overall Adverse Events

The following section reviews overall and specific adverse events in the Broad Dataset (analysis of results to 01 July 2012). The patterns observed in the Placebo-controlled Studies Dataset and the Pooled Renal Impairment Dataset were similar to that observed in the Broad Dataset (adjusting for differences in duration of exposure). For overall summary of adverse events in the Placebo-controlled Studies Dataset and in the Pooled Renal Impairment Dataset, see Attachment 13 and Attachment 14.

6.2.1. Summary of Adverse Events

In the Broad Dataset, the incidence of subjects who experienced any adverse event was similar across groups (Table 8). The incidence of adverse events considered related to study drug by the investigator was higher in the canagliflozin 100 mg and 300 mg groups compared with the non-canagliflozin group. These differences largely reflected a higher incidence of adverse events related to osmotic diuresis (eg, pollakiuria [ie frequency] or thirst) and a higher incidence of adverse events related to female or male genital mycotic infections in the canagliflozin groups. The incidence of discontinuations due to adverse events was higher in the canagliflozin groups relative to the non-canagliflozin group, with no notable difference in the incidence of serious adverse events, serious adverse events leading to discontinuation, or deaths. The incidence of subjects with serious adverse events that were considered related to study drug was also low, with similar incidences in the combined canagliflozin and non-canagliflozin groups.

Table 8: Overall Summary of Adverse Events in Broad Dataset (through 01 July 2012)

Number (%) of subjects with at least one adverse event of following types	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)
Any adverse events	2473 (75.8)	2369 (76.6)	2375 (77.0)	4744 (76.8)
Adverse events leading to discontinuation	164 (5.0)	173 (5.6)	224 (7.3)	397 (6.4)
Adverse events related to study drug[a]	711 (21.8)	910 (29.4)	1037 (33.6)	1947 (31.5)
Adverse events related to study drug[a] and leading to discontinuation	70 (2.1)	110 (3.6)	142 (4.6)	252 (4.1)
Serious adverse events	445 (13.6)	417 (13.5)	406 (13.2)	823 (13.3)
Serious adverse events leading to discontinuation	71 (2.2)	63 (2.0)	52 (1.7)	115 (1.9)
Serious adverse events related to study drug[a]	27 (0.8)	35 (1.1)	33 (1.1)	68 (1.1)
Serious adverse events related to study drug[a] and leading to discontinuation	10 (0.3)	17 (0.5)	14 (0.5)	31 (0.5)
Deaths	37 (1.1)	25 (0.8)	24 (0.8)	49 (0.8)

[a] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.

Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of rescue medication.

Cross-reference: tae00r0401jul12rae1.rtf generated by rae1.sas, 17AUG2012 15:55

6.2.2. Incidence of Specific Adverse Events

In the Broad Dataset, specific adverse events that were reported in at least 2% of subjects in any treatment group are presented in Table 9. Adverse events that were common (ie, occurred in at least 5% of subjects in the combined canagliflozin group or in the non-canagliflozin group) were diarrhea, nasopharyngitis, upper respiratory tract infection, UTI, hypoglycemia, back pain and headache. Of the common adverse events, only the adverse events of UTI and back pain occurred with a higher incidence in the combined canagliflozin group relative to the non-canagliflozin group. The adverse event of UTI was reported in 6.9% of subjects in the combined canagliflozin group and in 5.9% of subjects in the non-canagliflozin group. Urinary tract infection adverse events are discussed in Section 6.3.2. The adverse event back pain was reported in 5.9% of subjects in the combined canagliflozin group and in 5.1% of subjects in the non-canagliflozin group; most other adverse events in the Musculoskeletal and connective tissue disorders System Organ Class (SOC) occurred slightly more commonly in the non-canagliflozin group. For the other adverse events, only small differences in incidence for the canagliflozin groups relative to the non-canagliflozin groups were seen.

In the analysis of the Broad Dataset (results through 01 July 2012), no overall imbalance in the incidence of adverse events in the Neoplasms benign, malignant and unspecified SOC was observed. However, imbalances were observed for 3 specific adverse events in this SOC (all with incidences of <2%): adverse events of thyroid neoplasms, basal carcinoma of the skin, and colonic adenoma. Additional analyses were conducted to assess the clinical relevance of these imbalances.

As noted, a higher incidence of the adverse event of thyroid neoplasm was seen in the canagliflozin groups relative to the non-canagliflozin group (3 [0.1%] and 5 [0.2%] subjects in

the canagliflozin 100 mg and 300 mg groups, respectively, and 1 (<0.1%) subject in the non-canagliflozin group). This imbalance appears to be largely due to the way in which similar thyroid nodular disorders, when reported with slight differences in verbatim terms, are coded in the MedDRA dictionary (eg, the reported term of "multiple nodules of the left lobe of the thyroid gland" is coded to the preferred term of thyroid neoplasm, while the reported term of multinodular goiter is coded to the preferred term of goiter). To address this, an analysis was conducted that includes all terms in both the Neoplasms benign, malignant and unspecified and in the Metabolism and nutrition disorders SOCs that reflect gross changes in the thyroid (eg, nodules or thyroid enlargement), including the terms of thyroid neoplasm, thyroid cyst, thyroid cancer, and goiter (see Attachment 15 for all terms). This analysis showed no notable difference in incidence of these structural thyroid disorders in the canagliflozin relative to the non-canagliflozin treatment group, with the 95% CI around the between-group difference including "0" (7 [0.2%] and 12 [0.4%] subjects in the canagliflozin 100 mg and 300 mg groups, respectively, and 8 [0.2%] subjects in the non-canagliflozin group). The time course of adverse event of thyroid neoplasm was also not suggestive of a drug relationship, with 6 of the 8 adverse events in the canagliflozin group occurring within 6 months of randomization (with no events in the placebo group in this time frame).

An imbalance in the adverse event of basal cell skin carcinoma was seen, with 14 (0.5%) and 15 (0.5%) subjects in the canagliflozin 100 mg and 300 mg groups, respectively, and 10 (0.3%) subjects in the non-canagliflozin group. The time frame of reporting of these adverse events was not suggestive of a drug-relationship with approximately half (14 of 29 events) of the events in the canagliflozin groups reported within 6 months of randomization, and 22 of 29 events reported within 12 months of randomization. The incidence of squamous cell carcinoma of the skin occurred at a lower rate in the canagliflozin groups (3 [<0.1%] and 2 [<0.1%] subjects in the canagliflozin 100 mg and 300 mg groups, respectively, and 6 [0.2%] subjects in the non-canagliflozin groups). A low incidence of adverse events of malignant melanoma was observed, with 3 subjects (<0.1%) and 1 subject (<0.1%) in the canagliflozin 100 mg and 300 mg groups, respectively, and 1 subject in the non-canagliflozin group (with additional single reports in the canagliflozin groups of adverse events of malignant melanoma in situ and metastatic malignant melanoma); a higher incidence of subjects with early pigmented lesions (melanocytic or dysplastic naevus) in the neoplasm SOC was seen in the non-canagliflozin groups (5 subjects [0.1%] in the non-canagliflozin group and 5 subjects [<0.1%] in the canagliflozin groups). An analysis of all skin cancer-related terms (see Attachment 15) was conducted that showed no overall imbalance (30 [1.0%] and 33 [1.1%] subjects in the canagliflozin 100 mg and 300 mg groups, respectively, and 29 [0.9%] subjects in the non-canagliflozin groups).

Finally, an imbalance in the incidence of the adverse event of colon adenoma was reported in the canagliflozin groups (3 [<0.1%] and 5 [0.2%] subjects in the canagliflozin 100 mg and 300 mg groups, respectively, and 1 [<0.1%] subject in the non-canagliflozin group). These events in the canagliflozin group were reported in a time frame not suggestive of drug-relationship (with 6 of 8 reported within 12 months of randomization). In addition, an analysis including all terms related to intestinal tumors (see Attachment 15) showed no imbalance: 6 (0.2%) and 14 (0.5%)

subjects in the canagliflozin 100 mg and 300 mg groups, respectively, and 13 (0.4%) subjects in the non-canagliflozin group with an intestinal tumor-related adverse event.

For results of specific adverse events in the Placebo-controlled Studies Dataset and the Pooled Renal Impairment Dataset, see Attachment 13 and Attachment 14, respectively.

Table 9: Adverse Events in At Least 2% of Subjects in Any Treatment Group by Body System and Preferred Term in Broad Dataset (through 01 July 2012)

Body System Or Organ Class Dictionary-Derived Term	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)
Total no. subjects with the adverse events	2473 (75.8)	2369 (76.6)	2375 (77.0)	4744 (76.8)
Ear and labyrinth disorders	146 (4.5)	108 (3.5)	108 (3.5)	216 (3.5)
Vertigo	73 (2.2)	58 (1.9)	63 (2.0)	121 (2.0)
Gastrointestinal disorders	724 (22.2)	748 (24.2)	735 (23.8)	1483 (24.0)
Constipation	78 (2.4)	95 (3.1)	92 (3.0)	187 (3.0)
Diarrhoea	213 (6.5)	159 (5.1)	215 (7.0)	374 (6.1)
Nausea	90 (2.8)	92 (3.0)	108 (3.5)	200 (3.2)
Toothache	43 (1.3)	61 (2.0)	47 (1.5)	108 (1.7)
General disorders and administration site conditions	412 (12.6)	416 (13.5)	438 (14.2)	854 (13.8)
Chest pain	52 (1.6)	61 (2.0)	48 (1.6)	109 (1.8)
Fatigue	81 (2.5)	87 (2.8)	83 (2.7)	170 (2.8)
Oedema peripheral	122 (3.7)	63 (2.0)	59 (1.9)	122 (2.0)
Pyrexia	58 (1.8)	51 (1.6)	66 (2.1)	117 (1.9)
Thirst	2 (0.1)	42 (1.4)	69 (2.2)	111 (1.8)
Infections and infestations	1343 (41.2)	1343 (43.4)	1326 (43.0)	2669 (43.2)
Bronchitis	129 (4.0)	116 (3.8)	111 (3.6)	227 (3.7)
Gastroenteritis	80 (2.5)	64 (2.1)	72 (2.3)	136 (2.2)
Influenza	122 (3.7)	134 (4.3)	121 (3.9)	255 (4.1)
Nasopharyngitis	328 (10.1)	313 (10.1)	298 (9.7)	611 (9.9)
Sinusitis	84 (2.6)	81 (2.6)	83 (2.7)	164 (2.7)
Upper respiratory tract infection	271 (8.3)	224 (7.2)	206 (6.7)	430 (7.0)
Urinary tract infection	194 (5.9)	217 (7.0)	210 (6.8)	427 (6.9)
Vulvovaginal mycotic infection	22 (0.7)	73 (2.4)	76 (2.5)	149 (2.4)
Blood creatine phosphokinase increased	64 (2.0)	30 (1.0)	28 (0.9)	58 (0.9)
Metabolism and nutrition disorders	559 (17.1)	448 (14.5)	451 (14.6)	899 (14.6)
Hyperglycemia	113 (3.5)	51 (1.6)	44 (1.4)	95 (1.5)
Hypoglycemia	290 (8.9)	239 (7.7)	256 (8.3)	495 (8.0)
Musculoskeletal and connective tissue disorders	732 (22.4)	700 (22.6)	691 (22.4)	1391 (22.5)
Arthralgia	173 (5.3)	152 (4.9)	121 (3.9)	273 (4.4)
Back pain	165 (5.1)	169 (5.5)	196 (6.4)	365 (5.9)
Musculoskeletal pain	81 (2.5)	69 (2.2)	72 (2.3)	141 (2.3)
Osteoarthritis	67 (2.1)	71 (2.3)	64 (2.1)	135 (2.2)
Pain in extremity	115 (3.5)	106 (3.4)	83 (2.7)	189 (3.1)
Nervous system disorders	485 (14.9)	485 (15.7)	502 (16.3)	987 (16.0)
Dizziness	47 (1.4)	45 (1.5)	65 (2.1)	110 (1.8)
Headache	183 (5.6)	146 (4.7)	165 (5.3)	311 (5.0)

Table 9: Adverse Events in At Least 2% of Subjects in Any Treatment Group by Body System and Preferred Term in Broad Dataset (through 01 July 2012)

Body System Or Organ Class Dictionary-Derived Term	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)
Renal and urinary disorders	222 (6.8)	354 (11.4)	360 (11.7)	714 (11.6)
Pollakiuria	34 (1.0)	117 (3.8)	137 (4.4)	254 (4.1)
Reproductive system and breast disorders	129 (4.0)	273 (8.8)	321 (10.4)	594 (9.6)
Balanitis	14 (0.4)	74 (2.4)	68 (2.2)	142 (2.3)
Vulvovaginal pruritus	7 (0.2)	44 (1.4)	62 (2.0)	106 (1.7)
Respiratory, thoracic and mediastinal disorders	394 (12.1)	356 (11.5)	332 (10.8)	688 (11.1)
Cough	131 (4.0)	120 (3.9)	99 (3.2)	219 (3.5)
Vascular disorders	270 (8.3)	219 (7.1)	234 (7.6)	453 (7.3)
Hypertension	152 (4.7)	84 (2.7)	68 (2.2)	152 (2.5)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events, regardless of rescue medication.
Cross-reference: tae03r0401jul12rae2.rtf generated by rae2.sas, 17AUG2012 15:57

6.2.3. Adverse Events Leading to Discontinuation

The incidence of adverse events leading to discontinuation in the Broad Dataset was higher in the canagliflozin 300 mg group (7.3%) relative to the canagliflozin 100 mg (5.6%) and non-canagliflozin (5.0%) groups. Adverse events that led to discontinuation of more than 0.2% of subjects in the canagliflozin 300 mg group were glomerular filtration rate decreased (11 [0.4%] subjects), renal impairment (11 [0.4%] subjects), and blood creatinine increased (9 [0.3%] subjects) (Table 10). A modestly higher incidence of discontinuations related to these adverse events (pooling terms reflecting reduced renal function [eg, adverse events of renal failure, renal impairment, blood creatinine increased, GFR decreased]) was seen in the canagliflozin 300 mg group, with a similar incidence in the canagliflozin 100 mg and non-canagliflozin groups, as discussed in Section 6.4.2.5. Follow-up eGFR information was obtained in all subjects who discontinued due to renal-related adverse events: a high proportion of these subjects had follow-up eGFR values that were at baseline or only modestly below baseline levels – with a similar small proportion in the canagliflozin and non-canagliflozin groups having persistent decreases.

For additional results from the Placebo-controlled Studies Dataset and the Pooled Renal Impairment Dataset, see Attachment 16 and Attachment 17, respectively.

Table 10: Adverse Events Leading to Treatment Discontinuation in At Least 0.2% of Subjects in Any Treatment Group in Broad Dataset (through 01 July 2012)

Body System Or Organ Class Dictionary-Derived Term	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)
Total no. subjects with the adverse events	164 (5.0)	173 (5.6)	224 (7.3)	397 (6.4)
Gastrointestinal disorders	27 (0.8)	27 (0.9)	22 (0.7)	49 (0.8)
Nausea	4 (0.1)	7 (0.2)	6 (0.2)	13 (0.2)
Infections and infestations	17 (0.5)	37 (1.2)	36 (1.2)	73 (1.2)
Urinary tract infection	2 (0.1)	10 (0.3)	5 (0.2)	15 (0.2)
Investigations	20 (0.6)	21 (0.7)	34 (1.1)	55 (0.9)
Blood creatinine increased	4 (0.1)	6 (0.2)	9 (0.3)	15 (0.2)
Glomerular filtration rate decreased	7 (0.2)	4 (0.1)	11 (0.4)	15 (0.2)
Renal and urinary disorders	9 (0.3)	14 (0.5)	27 (0.9)	41 (0.7)
Pollakiuria	0	4 (0.1)	7 (0.2)	11 (0.2)
Renal impairment	6 (0.2)	3 (0.1)	11 (0.4)	14 (0.2)
Reproductive system and breast disorders	4 (0.1)	12 (0.4)	24 (0.8)	36 (0.6)
Balanoposthitis	0	5 (0.2)	8 (0.3)	13 (0.2)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events, regardless of use of rescue medication.
Cross-reference: dae06othacds3lt2rae2a.rtf generated by rae2a.sas, 13SEP2012 11:37

6.2.4. Serious Adverse Events and Death

The overall incidence of serious adverse events was similar in the combined canagliflozin group compared with the non-canagliflozin group in the Broad Dataset (results through 01 July 2012), with similar incidences in the canagliflozin 100 mg and 300 mg groups (Table 11). No individual serious adverse event terms had an incidence of more than 0.5% in any group and most having an incidence of less than 0.1%.

For results from the Placebo-controlled Studies Dataset and the Pooled Renal Impairment Dataset, see Attachment 18 and Attachment 19, respectively.

Table 11: Serious Adverse Events in At Least 0.2% of Subjects in Any Treatment Group in Broad Dataset (through 01 July 2012)

Body System Or Organ Class Dictionary-Derived Term	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)
Total no. subjects with the adverse events	445 (13.6)	417 (13.5)	406 (13.2)	823 (13.3)
Cardiac disorders	107 (3.3)	78 (2.5)	76 (2.5)	154 (2.5)
Angina pectoris	12 (0.4)	10 (0.3)	11 (0.4)	21 (0.3)
Angina unstable	7 (0.2)	4 (0.1)	10 (0.3)	14 (0.2)
Atrial fibrillation	8 (0.2)	10 (0.3)	8 (0.3)	18 (0.3)
Cardiac failure	8 (0.2)	3 (0.1)	3 (0.1)	6 (0.1)
Cardiac failure congestive	9 (0.3)	5 (0.2)	7 (0.2)	12 (0.2)
Coronary artery disease	15 (0.5)	11 (0.4)	12 (0.4)	23 (0.4)
Myocardial infarction	9 (0.3)	7 (0.2)	6 (0.2)	13 (0.2)
General disorders and administration site conditions	34 (1.0)	27 (0.9)	27 (0.9)	54 (0.9)
Chest pain	11 (0.3)	13 (0.4)	8 (0.3)	21 (0.3)
Non-cardiac chest pain	7 (0.2)	5 (0.2)	3 (0.1)	8 (0.1)
Hepatobiliary disorders	14 (0.4)	17 (0.5)	13 (0.4)	30 (0.5)
Cholelithiasis	7 (0.2)	2 (0.1)	2 (0.1)	4 (0.1)
Infections and infestations	88 (2.7)	86 (2.8)	72 (2.3)	158 (2.6)
Cellulitis	9 (0.3)	6 (0.2)	6 (0.2)	12 (0.2)
Gangrene	2 (0.1)	7 (0.2)	0	7 (0.1)
Gastroenteritis	7 (0.2)	3 (0.1)	6 (0.2)	9 (0.1)
Pneumonia	14 (0.4)	10 (0.3)	12 (0.4)	22 (0.4)
Sepsis	7 (0.2)	5 (0.2)	1 (<0.1)	6 (0.1)
Urinary tract infection	8 (0.2)	11 (0.4)	7 (0.2)	18 (0.3)
Musculoskeletal and connective tissue disorders	36 (1.1)	33 (1.1)	24 (0.8)	57 (0.9)
Osteoarthritis	5 (0.2)	13 (0.4)	8 (0.3)	21 (0.3)
Nervous system disorders	37 (1.1)	37 (1.2)	48 (1.6)	85 (1.4)
Transient ischaemic attack	10 (0.3)	8 (0.3)	11 (0.4)	19 (0.3)
Renal and urinary disorders	24 (0.7)	29 (0.9)	27 (0.9)	56 (0.9)
Renal failure acute	7 (0.2)	9 (0.3)	6 (0.2)	15 (0.2)
Respiratory, thoracic and mediastinal disorders	33 (1.0)	26 (0.8)	19 (0.6)	45 (0.7)
Pulmonary embolism	5 (0.2)	3 (0.1)	7 (0.2)	10 (0.2)
Skin and subcutaneous tissue disorders	6 (0.2)	16 (0.5)	15 (0.5)	31 (0.5)
Diabetic foot	2 (0.1)	3 (0.1)	7 (0.2)	10 (0.2)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events, regardless of rescue medication.

Cross-reference: dae13bothacds3lt2_t1.rtf generated by dae13bothacds3lt2.sas, 27SEP2012 20:36

The incidence of adverse events with an outcome of death was slightly lower in the canagliflozin groups relative to the non-canagliflozin group. The majority of adverse events with an outcome of death were in the Cardiac disorders, General disorders and administration site conditions, Infections and infestations, Nervous systems disorders, and Respiratory, thoracic and mediastinal disorders SOCs (Table 12), without a discernible pattern.

Table 12: Adverse Events with Outcome of Death Reported in >1 Subject in Any Treatment Group in Broad Dataset (through 01 July 2012)

Body System Or Organ Class Dictionary-Derived Term	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)
Total no. subjects with the adverse events	37 (1.1)	25 (0.8)	24 (0.8)	49 (0.8)
Cardiac disorders	15 (0.5)	9 (0.3)	7 (0.2)	16 (0.3)
Acute myocardial infarction	2 (0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Cardiac arrest	3 (0.1)	2 (0.1)	3 (0.1)	5 (0.1)
Cardio-respiratory arrest	2 (0.1)	0	0	0
Myocardial infarction	2 (0.1)	2 (0.1)	0	2 (<0.1)
General disorders and administration site conditions	6 (0.2)	1 (<0.1)	6 (0.2)	7 (0.1)
Death	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Sudden cardiac death	1 (<0.1)	0	2 (0.1)	2 (<0.1)
Sudden death	4 (0.1)	0	2 (0.1)	2 (<0.1)
Infections and infestations	5 (0.2)	3 (0.1)	2 (0.1)	5 (0.1)
Sepsis	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Septic shock	2 (0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (0.2)	3 (0.1)	2 (0.1)	5 (0.1)
Bronchial carcinoma	2 (0.1)	0	0	0
Pancreatic carcinoma	2 (0.1)	1 (<0.1)	0	1 (<0.1)
Nervous system disorders	4 (0.1)	4 (0.1)	5 (0.2)	9 (0.1)
Cerebrovascular accident	0	1 (<0.1)	2 (0.1)	3 (<0.1)
Coma	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Renal and urinary disorders	1 (<0.1)	2 (0.1)	1 (<0.1)	3 (<0.1)
Renal failure acute	1 (<0.1)	2 (0.1)	1 (<0.1)	3 (<0.1)
Respiratory, thoracic and mediastinal disorders	5 (0.2)	5 (0.2)	2 (0.1)	7 (0.1)
Pulmonary embolism	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Respiratory failure	2 (0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events, regardless of rescue medication.
Cross-reference: tae56rdeath0401jul12rae2.rtf generated by rae2.sas, 07SEP2012 12:03

6.3. Review of Specific Adverse Events Assessed as Adverse Drug Reactions

6.3.1. Overview

An assessment of the pooled databases (Table 6) was performed with an initial focus on the Placebo-controlled Studies Dataset, followed by review of the Broad Dataset, to identify ADRs. Adverse events in the Placebo-controlled Studies Dataset occurring at an incidence that met the following criteria were identified as potential ADRs: incidence of ≥2% and more common with canagliflozin relative to placebo. Adverse events identified as potential ADRs were then examined with regard to consistency across datasets and biologic plausibility; based upon this assessment, the following were determined to be drug-related (ie, ADRs): adverse events of UTI, female and male genital infections (vulvovaginitis, balanitis/balanoposthitis), adverse events reflecting osmotic diuresis (polyuria or pollakiuria [ie, frequency], and thirst), and adverse events of constipation. Only 1 adverse event, back pain, met the criteria above (ie, ≥2% and more common with canagliflozin relative to placebo) and was not considered as an ADR for the following reasons. In the Broad Dataset, the adverse event of back pain occurred with only a slightly higher incidence in the combined canagliflozin group relative to the non-canagliflozin group (5.9% and 5.1%, respectively) and other common adverse events (such as arthralgia, musculoskeletal pain, or pain in extremity) in the Musculoskeletal and connective tissue disorders SOC occurring slightly more frequently in the non-canagliflozin group. In conjunction with the lack of biological plausibility, this suggested that back pain was unlikely to be a canagliflozin ADR. The list of canagliflozin ADRs with an incidence of at least 2% is provided in Table 13.

Table 13: Adverse Reactions in ≥2% of Canagliflozin-Treated Subjects in Placebo-controlled Studies Dataset

System Organ Class Adverse Reaction	Placebo N=646 (n) %	CANA 100 mg N=833 (n) %	CANA 300 mg N=834 (n) %
Gastrointestinal Disorders			
Constipation	6 (0.9)	15 (1.8)	19 (2.3)
Thirst	1 (0.2)	23 (2.8)	19 (2.3)
Renal and Urinary Disorders			
Polyuria or Pollakiuria	5 (0.8)	44 (5.3)	38 (4.6)
Urinary tract infection	26 (4.0)	49 (5.9)	36 (4.3)
Reproductive System and Breast Disorders			
Balanitis or Balanoposthitis	2 (0.6)	17 (4.2)	15 (3.7)
Vulvovaginal candidiasis	10 (3.2)	44 (10.4)	49 (11.4)

[a] Percentages calculated with the number of male subjects in each group as denominator and the number of male subjects experiencing at least one adverse event
[b] Percentages calculated with the number of female subjects in each group as denominator and the number of female subjects experiencing at least one adverse event

In addition to those included in Table 13, review of results from the Broad Dataset identified several other likely ADRs, which were not clearly seen (ie, minimal between-group differences) in the Placebo-controlled Studies Dataset; these included events that were uncommon (<2%), but

appeared to be associated with canagliflozin (urticaria and rash), and events that may have been more commonly observed with canagliflozin relative to control in the more vulnerable population included in the Broad Dataset such as adverse events reflecting reduced intravascular volume. Finally, review of individual studies showed that events of hypoglycemia occurred at a higher rate when canagliflozin was co-administered with insulin or a SU (with or without metformin); hence, such events were also identified as ADRs.

The following sections review each of the identified ADRs for canagliflozin.

6.3.2. Urinary Tract Infections

6.3.2.1. Phase 2 Studies: Urine Culture Results

To examine the impact of canagliflozin on microorganism growth in a Phase 2 study in subjects with T2DM (DIA2001), a mid-stream clean-catch urine specimen was collected for culture at baseline and Week 12/end-of-treatment visit in all subjects. Bacteriuria was defined as any bacteria $\geq 10^5$ colony-forming units (CFUs)/mL isolated from the urine culture. Candiduria was identified when $\geq 10^3$ CFU/mL of a *Candida* species was isolated.

Urine cultures were available for 371 (82.3%) of 451 subjects at baseline, with bacteriuria present in 24 (6.5%). Among subjects with urine cultures at Week 12 who had negative cultures at baseline, 3 (3.0%) of 100 non-canagliflozin treated subjects and 10 (4.0%) of 247 subjects who received canagliflozin, developed bacteriuria at Week 12, without evidence for dose-dependency. *Escherichia coli* was the most common organism isolated at baseline and at end-study.

6.3.2.2. Phase 3 Results

6.3.2.2.1. Data Collection and Analysis

In the canagliflozin Phase 3 program, for adverse events of UTIs, investigators were instructed to complete a supplemental electronic case report form (eCRF) page that captured additional information related to the diagnosis and associated signs or symptoms of the adverse event (eg, method of diagnosis, specific signs and/or symptoms associated with the UTI).

A pre-specified standard query using a list of adverse event terms reflecting urinary tract infections (eg, cystitis, urinary tract infection, pyelonephritis, kidney infection) was applied, with terms grouped for analysis to assess the overall incidence of UTI adverse events. Similarly, a pre-specified query using a list of adverse events consistent with upper tract UTIs was also applied (eg, pyelonephritis or acute pyelonephritis), with terms grouped for analysis.

6.3.2.2.2. Incidence and Characteristics of Adverse Events of UTI

Broad Dataset

In the Broad Dataset (results through 01 July 2012), a small increase in the incidence of adverse events of UTI with the canagliflozin relative to non-canagliflozin treated subjects was observed: 8.2% and 8.1% in canagliflozin 100 mg and 300 mg groups, respectively, and 6.7% in

non-canagliflozin group (Table 14). The incidence of serious adverse events of UTI was low and similar in the canagliflozin groups relative to the non-canagliflozin group. The incidence of upper tract UTI adverse events was low, higher in the combined canagliflozin group (30 [0.5%]) than in the non-canagliflozin group (11 [0.3%]), related to a higher incidence in the canagliflozin 100 mg group. With regard to specific adverse events of upper UTI, the number of subjects with events reflecting acute upper tract infection (ie, urosepsis or acute pyelonephritis or pyelonephritis) was similar across groups, with a higher number of subjects in the canagliflozin groups with the adverse event of pyelonephritis chronic (8 in canagliflozin treatment groups and 1 in non-canagliflozin). Seven out of 8 events of pyelonephritis chronic were asymptomatic: 4 of them were reported based on the ultrasound findings (studies done to evaluate for nephrolithiasis, UTI, or neoplasm), and 3 of the 8 subjects with an event of chronic pyelonephritis had a medical history of chronic pyelonephritis. The adverse events of pyelonephritis chronic were assessed by the investigators as mild or moderate in intensity, not reported as serious adverse events, did not lead to study discontinuation, and none were considered as related to study drug by the investigator.

For adverse events of UTI, the investigator-assessed intensity (ie, mild/moderate or severe) was similar in the canagliflozin and non-canagliflozin groups, and the median duration of symptoms for the UTI adverse events were similar in the canagliflozin groups and the non-canagliflozin group (12.0 days in the canagliflozin 100 mg group, 10.5 days in the canagliflozin 300 mg group, and 11.0 days in the non-canagliflozin group). Recurrence rates were also similar in the combined canagliflozin and non-canagliflozin groups for symptomatic UTI adverse events: 19.9% and 23.8% of subjects, respectively, had >1 such UTI adverse event.

Table 14: Overall Summary of Urinary Tract Infection Adverse Events in Broad Dataset (through 01 July 2012)

Number (%) of subjects with at least one UTI adverse event of following types:	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)	All CANA Minus -- All Non-CANA - Diff(%)	95%CI[a]
Any adverse event	218 (6.7)	254 (8.2)	250 (8.1)	504 (8.2)	1.5	(0.4; 2.6)
Incidence rate per 1000 subject-years exposure	*54.17*	*62.32*	*62.70*	*62.51*		
Adverse event leading to discontinuation	4 (0.1)	11 (0.4)	6 (0.2)	17 (0.3)	0.2	(-0.0; 0.4)
Adverse event related to study drug[b]	106 (3.2)	152 (4.9)	148 (4.8)	300 (4.9)	1.6	(0.8; 2.4)
Serious adverse event	12 (0.4)	16 (0.5)	8 (0.3)	24 (0.4)	0.0	(-0.3; 0.3)
Upper tract UTI adverse event	11 (0.3)	20 (0.6)	10 (0.3)	30 (0.5)	0.2	(-0.1; 0.4)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

[b] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.

Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.

Note: Exposure adjusted incidence rates are per 1000 subject-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total subject-year exposure for all safety subjects in each treatment group).

Cross-reference: tae13a0401jul12raeuti1overallci.rtf generated by raeuti1overallci.sas, 03DEC2012 09:34; tae130401jul12raeutioverall.rtf generated by raeutioverall.sas, 17AUG2012 16:03;tae14uti0401jul12raeuti.rtf generated by raeuti.sas, 28AUG2012 12:17

The results in the Placebo-controlled Studies Dataset were generally similar to those described above, considering differences in duration of exposure. The incidence of the adverse event of UTI was increased with canagliflozin, in a non-dose dependent fashion (5.9% and 4.3% in the canagliflozin 100 mg and 300 mg groups, respectively, and 4.0% in the placebo group).

Pooled Renal Impairment Dataset

A higher incidence of the adverse event of UTI was seen with canagliflozin 300 mg, with no notable difference for canagliflozin 100 mg, relative to placebo: 6.2% and 7.4% in the canagliflozin 100 mg and 300 mg groups, respectively, and 6.0% in the placebo group (Table 15). With regard to the pattern, investigator-assessed intensity (ie, mild/moderate or severe) was similar in the canagliflozin and placebo groups. The median duration of these events was similar in the canagliflozin and placebo groups (11 and 13 days, respectively), and the recurrence rate of symptomatic UTI was <10% in the combined canagliflozin group and lower than the recurrence rate observed in the placebo group. There were 2 upper tract adverse events in the canagliflozin group and one reported in the placebo group. One serious adverse event of UTI was reported in the combined canagliflozin group and 3 in the placebo group.

Table 15: Overall Summary of Urinary Tract Infection Adverse Events in Renal Impairment Dataset

Number (%) of subjects with at least one UTI adverse event of following types:	Placebo (N=382) n (%)	CANA 100 mg (N=338) n (%)	CANA 300 mg (N=365) n (%)	All CANA (N=703) n (%)	All CANA Minus ---- Placebo ---- Diff(%)	95%CI[a]
Any adverse event	23 (6.0)	21 (6.2)	27 (7.4)	48 (6.8)	0.8	(-2.4; 4.0)
Adverse event leading to discontinuation	2 (0.5)	1 (0.3)	0	1 (0.1)	-0.4	(-1.4; 0.6)
Adverse event related to study drug[b]	14 (3.7)	12 (3.6)	17 (4.7)	29 (4.1)	0.5	(-2.1; 3.1)
Serious adverse event	3 (0.8)	1 (0.3)	0	1 (0.1)	-0.6	(-1.8; 0.5)
Upper tract UTI adverse event	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.3)	0.0	(-0.8; 0.9)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.
[b] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.
Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.
Cross-reference: tae13a0401jul12raeuti1overallci_02.rtf generated by raeuti1overallci_02.sas, 02DEC2012 16:08

6.3.2.3. Summary

In Phase 2 studies, no substantive increase in the occurrence of bacteriuria was seen with canagliflozin treatment. In Phase 3 studies, a small increase in the incidence of non-serious adverse events of UTI was seen with canagliflozin; these UTIs did not appear to be more severe, have a different duration, or an increased recurrence rate, relative to the comparator group. In conjunction with the small increase in incidence, these observations would suggest this ADR will be clinically manageable.

6.3.3. Genital Mycotic Infections

6.3.3.1. Phase 2 Studies: Results of Vaginal Cultures

In the Phase 2b study dose-range finding study in subjects with T2DM (DIA2001), vaginal swabs for *Candida* cultures were collected from female subjects at baseline and Week 12/end-of-

treatment visit, and during the study if symptoms consistent with vulvovaginal mycotic infection occurred.

In the DIA2001 study, vaginal cultures collected through self-administered swabs were available for 198 (92%) female subjects at baseline; 23 (12%) were positive for *Candida* species and *C. glabrata* was the most common isolate (observed in 14 of the 23 women). This is consistent with the published data on prevalence of *C. glabrata* in women with T2DM (Ray 2007). Of those with negative cultures at baseline, 31% of subjects in the pooled canagliflozin group (in a non-dose-related fashion) and 14% of subjects in the pooled placebo/sitagliptin group converted to positive at Week 12.

This study also showed that all women who had an adverse event related to vulvovaginitis (16 subjects) who had a concurrent vaginal swab culture (9 subjects) were positive for a *Candida* species. These observations indicate that the adverse vulvovaginal events observed with canagliflozin are likely due to genital mycotic infections.

6.3.3.2. Phase 3 Results

6.3.3.2.1. Female Genital Mycotic Infection

6.3.3.2.1.1. Data Collection and Analysis

To capture relevant information regarding genital mycotic infections, including diagnosis and treatment patterns, investigators were instructed to complete a supplemental eCRF page capturing information related to the onset of the event, methods of diagnosis, symptoms, treatment (self-prescribed or health care provider-prescribed), and time to symptoms resolution.

For analysis, a pre-specified query using a list of terms consistent with a female genital mycotic infection (vulvovaginitis, candidal vulvovaginitis, genital candidiasis, genital infection fungal, vaginal infection, urogenital infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vaginal inflammation) was constructed, with terms grouped for analysis.

6.3.3.2.1.2. Incidence and Characteristics of Female Genital Mycotic Infections

In the Broad Dataset (through 01 July 2012), the incidence of female genital mycotic infection adverse events (incidence based upon analysis in female subjects only) was higher in the combined canagliflozin group (14.3%) compared with the placebo group (3.1%) and with a slightly higher incidence in the canagliflozin 100 mg group (14.7%) compared with the canagliflozin 300 mg group (13.9%) (Table 16). This incidence is based upon a mean duration of exposure of 68 weeks in the canagliflozin and 64 weeks in the non-canagliflozin groups (see Section 6.1.2)

Table 16: Overall Summary of Female Genital Mycotic Infection Adverse Events in Broad Dataset (through 01 July 2012)

Number (%) of subjects with at least one adverse event of following types:	All Non-CANA (N=1338) n (%)	CANA 100 mg (N=1289) n (%)	CANA 300 mg (N=1319) n (%)	All CANA (N=2608) n (%)	All CANA Minus -- All Non-CANA - Diff(%)	95%CI[a]
Any vulvovaginitis	42 (3.1)	190 (14.7)	184 (13.9)	374 (14.3)	11.2	(9.5; 12.9)
Incidence rate per 1000 subject-years exposure	*26.96*	*118.90*	*112.87*	*115.85*		
Vulvovaginitis leading to discontinuation	0	13 (1.0)	17 (1.3)	30 (1.2)	1.2	(0.7; 1.6)
Vulvovaginitis related to study drug[b]	28 (2.1)	147 (11.4)	153 (11.6)	300 (11.5)	9.4	(7.9; 10.9)
Serious adverse events of vulvovaginitis	0	0	0	0	0.0	(-0.1; 0.1)

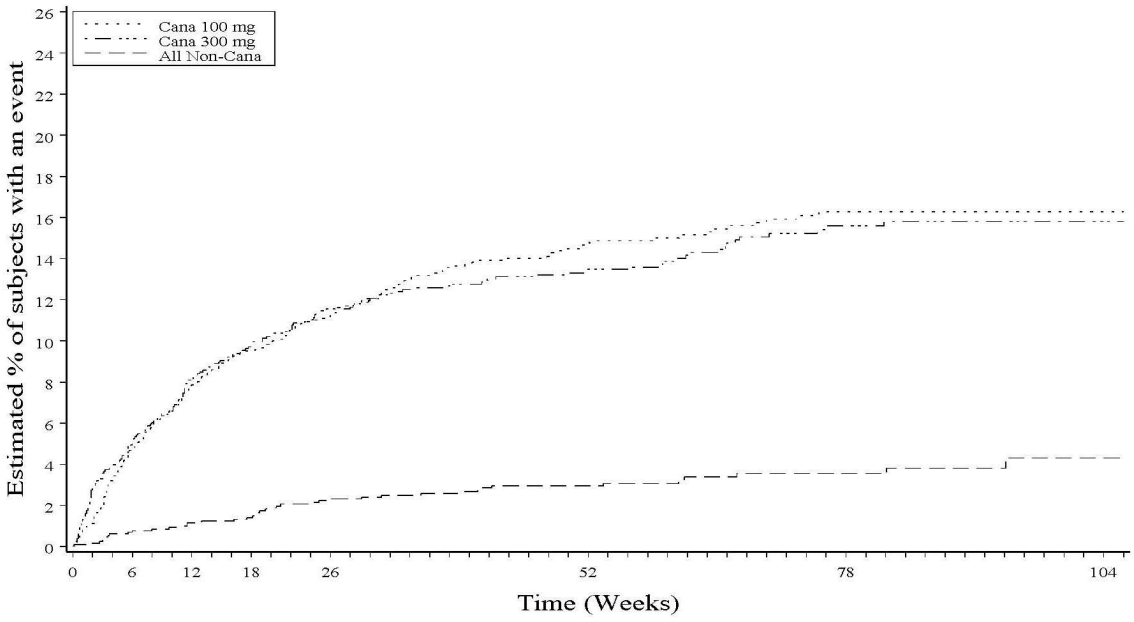
[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.
[b] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.
Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.
Note: Exposure adjusted incidence rates are per 1000 subject-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total subject-year exposure for all safety subjects in each treatment group).
Cross-reference: tae21bvvac04msuraevv_overall_mycnos.rtf generated by raevv_overall_mycnos.sas, 02DEC2012 18:54, tae22vvac04msuraevv_mycnos1.rtf generated by raevv_mycnos1.sas, 19NOV2012 16:12

Canagliflozin-treated women with a female genital mycotic infection adverse event, relative to female subjects who did not have a female genital mycotic infection, were of similar age (mean age of 58.5 years and 59.4 years, respectively), were more likely to be pre-menopausal (19.8% compared with 15.3%), more likely to have a prior history of yeast infections (27.3% compared with 9.4%), and had a slightly higher median BMI (34.0 kg/m^2 compared with 31.7 kg/m^2). No differences were noted in baseline HbA_{1c} between women in the canagliflozin groups with a mycotic genital infection with relative to those without a mycotic genital infection.

The majority of events were diagnosed based on the clinical history (either diagnosed by a healthcare provider or self-diagnosed by the subject herself), with a minority of subjects (in 17.8% of female genital mycotic infection adverse events) undergoing a pelvic exam and/or a vaginal fungal culture to confirm the clinical diagnosis. In general, these adverse events were assessed by the investigator as mild or moderate in intensity, with 11 (0.4%) subjects experiencing severe events. The highest rate of occurrence of these adverse events was in the initial 4 months of treatment (Figure 23), and with no serious adverse events reported (Table 16). In the combined canagliflozin group, these events were generally treated by the health care professional (approximately 65% of treated events) or by the subject herself (approximately 35%

of treated adverse events) without discontinuing study drug. Overall, 73.2% were treated with antifungal agents, 1.8% were treated with antibacterial agents, 5.2% were treated with antifungal and antibacterial agents, and 19.8% were not treated. With regard to the route of administration, 36.7% subjects were treated with topical agents only, 27.8% were treated with oral agents only, and 15.6% were treated with both oral and topical agents. The response to antifungal treatment appeared to be generally similar with the median time to symptom resolution only slightly longer in the canagliflozin 300 mg group (8.7 days) relative to the canagliflozin 100 mg (7.0 days) and the non-canagliflozin groups (6.5 days). Discontinuation due to these events was infrequent: 1.2% of all female subjects discontinued canagliflozin due to genital mycotic infections (Table 16); 4.6% of women in the combined canagliflozin group had more than 1 vulvovaginitis event and 0.7% of female subjects in the non-canagliflozin group had more than 1 event.

Figure 23: Kaplan-Meier Plot of Time to the First Female Genital Mycotic Infection in Broad Dataset (through 01 July 2012)



The incidence in the Placebo-controlled Studies Dataset was generally similar as described above, with the slightly lower incidence reflecting the shorter duration of exposure (reported in 10.4% and 11.4% in the canagliflozin 100 mg and 300 mg groups, respectively, and 3.2% in the placebo group).

6.3.3.2.1.3. Summary

In summary, female genital mycotic infections are an ADR to canagliflozin; this adverse reaction is manageable, responding to standard topical or oral antifungal therapies, infrequently leading to discontinuation of canagliflozin therapy.

6.3.3.2.2. Male Genital Mycotic Infections

6.3.3.2.2.1. Data Collection and Analysis

To capture relevant information regarding genital mycotic infections in men, the investigators were instructed to complete a specific eCRF designed to capture information related to signs and symptoms of the male genital mycotic adverse event, involvement of foreskin (if not circumcised), if culture was performed with results (if applicable), treatment prescribed (self-prescribed or health care provider-prescribed), and time to resolution of symptoms associated with the event after treatment was initiated, and suspected etiology.

For analysis, a pre-specified query using a list of terms consistent with a male genital mycotic infection (balanitis, balanitis candida, balanoposthitis, balanoposthitis infective, erosive balanitis, gangrenous balanitis, genital candidiasis, genital infection, genital infection fungal, penile candida, penile infection, posthitis) was constructed, with terms grouped for analysis.

6.3.3.2.2.2. Incidence and Characteristics of Male Genital Mycotic Infections

In the Broad Dataset (through 01 July 2012), an increased incidence of male genital mycotic infection adverse events (incidence among male subjects) was seen with canagliflozin treatment (7.3% and 9.3% in the 100 mg and 300 mg groups, respectively), with 1.6% of male subjects in the non-canagliflozin group having an adverse event of genital mycotic infection (Table 17).

Table 17: Overall Summary of Male Genital Infection Adverse Events in the Broad Dataset (through 01 July 2012)

Number (%) of subjects with at least one adverse event of following types:	All Non-CANA (N=1924) n (%)	CANA 100 mg (N=1803) n (%)	CANA 300 mg (N=1766) n (%)	All CANA (N=3569) n (%)	All CANA Minus -- All Non-CANA - Diff(%)	95%CI[a]
Any male genital infections	30 (1.6)	131 (7.3)	164 (9.3)	295 (8.3)	6.7	(5.6; 7.8)
Incidence rate per 1000 subject-years exposure	*12.16*	*52.88*	*69.58*	*61.02*		
Male genital infections leading to discontinuation	0	14 (0.8)	19 (1.1)	33 (0.9)	0.9	(0.6; 1.3)
Male genital infections related to study drug [b]	22 (1.1)	110 (6.1)	145 (8.2)	255 (7.1)	6.0	(5.0; 7.0)
Serious adverse events of male genital infection	0	1 (0.1)	1 (0.1)	2 (0.1)	0.1	(-0.1; 0.2)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

[b] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.

Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.

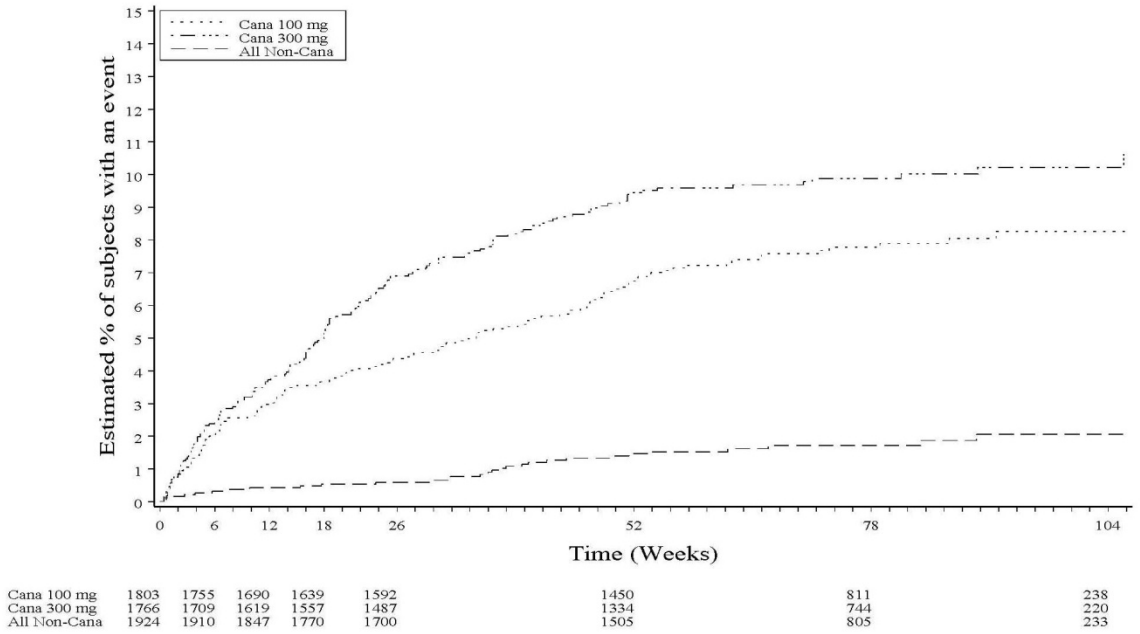
Note: Exposure adjusted incidence rates are per 1000 subject-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total subject-year exposure for all safety subjects in each treatment group).

Cross-reference: tae01mgac04msuraemg_overall0.rtf generated by raemg_overall0.sas, 04DEC2012 10:17, tae02mgac04msuraemg1.rtf generated by raemg1.sas, 05OCT2012 09:25

In the combined canagliflozin group, adverse events of male genital mycotic infections were more commonly reported in men who were uncircumcised than in circumcised males: 10.8% (255/2358) and 3.4% (38/1131), respectively. In the combined canagliflozin group, a prior medical history of balanitis/balanoposthitis was present in 18.6% of men who reported an adverse event of a male genital mycotic infection compared with only 2.7% of men who did not report such an adverse event. Men in the combined canagliflozin group experiencing an adverse event of a male genital mycotic infection compared with men not having this adverse event did not notably differ in baseline HbA_{1c}, age, or BMI. In the Broad Dataset, 7 events of male genital mycotic infections were reported as severe in intensity. Two of the male genital mycotic infections were serious (Table 17) related to the occurrence of phimosis, with hospitalization for circumcision surgery.

In general, the male genital infection adverse events were mild to moderate in intensity and were not associated with interruption of study drug. In most cases the diagnosis was made on a clinical basis without a microbiologic culture being done. In the combined canagliflozin group, male genital mycotic infections were treated by a healthcare professional for the majority of the subjects and most commonly treated with a topical antifungal agent. A small proportion (0.9%) of subjects in the combined canagliflozin group with balanoposthitis discontinued due to the adverse event. Overall, 15.3% of the men in the combined canagliflozin group reporting an adverse event of a genital mycotic infection (and 1.3% of male subjects overall) had more than 1 event. The incidence of male genital mycotic infections increased at a generally consistent rate throughout the first year of treatment, after which the incident rate appeared to plateau (Figure 24).

Figure 24: Kaplan-Meier Plot of Time to the First Male Genital Infection Adverse Event in Broad Dataset (through 01 July 2012)



In the analysis of the Broad Dataset (through 01 July 2012), in the combined canagliflozin groups, 18 (0.3%) subjects (8 subjects in the 100 mg group and 10 subjects in the 300 mg group) were reported to have had circumcision performed (due to an adverse event of phimosis and/or balanitis/balanoposthitis). The majority of procedures were conducted as out-patient surgery and did not require hospitalization.

The incidence of male genital mycotic infections in the Placebo-controlled Studies Dataset was lower, reflecting the shorter duration of exposure (4.2% and 3.7% in the canagliflozin 100 mg and 300 mg groups, respectively, and 0.6% in the placebo group).

6.3.3.2.2.3. Summary

Overall, male genital mycotic infections are an ADR observed with canagliflozin that is generally manageable with usual antifungal treatments, can occasionally require discontinuation and infrequently leads to complications such as phimosis that can require surgical intervention with circumcision.

6.3.4. Osmotic Diuresis-Related Adverse Events

6.3.4.1. Introduction and Data Analysis

By increasing urinary glucose, canagliflozin induces an osmotic diuresis with an increase in urine output. In the multiple dose Phase 1 study in subjects with T2DM (NAP1002), a transient modest increase in urine output was observed (with doses of 100 mg per day and above) over the first days of treatment that was no longer evident by Day 16.

The osmotic diuresis may lead to adverse events directly reflecting the increase in urine output, such as urinary frequency and/or urgency or an increase in urine output. In addition, the increase in fluid loss may lead to a symptoms reflecting increased thirst or fluid intake, with adverse event terms such as thirst, polydipsia, dry mouth, throat dry, or tongue dry. The diuretic effect related to the osmotic diuresis may also reduce intravascular volume. In this section, adverse events reflecting osmotic diuresis-related symptoms of increased frequency or urine volume or of increased fluid intake are described and in Section 6.3.5, adverse events reflecting decreased intravascular volume are presented.

In order to fully evaluate adverse events related to the osmotic diuresis, a pre-specified query including a list of adverse event preferred terms reflecting increased urine output, frequency, or thirst was applied so as to better characterize the overall incidence and profile (eg, onset, intensity, discontinuation rate) of such adverse events. Since some adverse events reflected an increase in urine output (ie, increased urinary urgency, frequency [pollakiuria] and/or urine output [polyuria], or an increase in nighttime micturition [nocturia]) and some adverse events reflected an increase in thirst (ie, thirst, dry mouth, dry tongue, or increased fluid intake [polydipsia]), in addition to the overall pooling of all terms for symptoms reflecting the osmotic diuresis, a categorical analysis based on preferred terms subsumed under the 2 key categories (ie, “polyuria/pollakiuria” or “thirst”) was performed.

Pooled summaries and analyses for adverse events associated with osmotic diuresis are presented for the Broad Dataset (through 01 July 2012) in Table 18; the incidences observed in the Placebo-controlled Studies Dataset were similar to those described below for the Broad Dataset. The incidence in the Renal Impairment Dataset is described later in this section.

6.3.4.2. Incidence and Characteristics of Osmotic Diuresis-Related Adverse Events

Broad Dataset

In the Broad Dataset, there was a higher incidence of osmotic diuresis-related adverse events in the combined canagliflozin group (7.6%) relative to the non-canagliflozin group (2.4%); the incidence was only slightly higher in the canagliflozin 300 mg relative to the canagliflozin 100 mg group. The most common preferred terms were adverse events of pollakiuria (ie, urinary frequency), thirst, and polyuria. The majority of the adverse events in both canagliflozin groups and the non-canagliflozin group were considered related to study drug by the investigator.

No subject had a serious osmotic diuresis-related adverse event. Two subjects in the canagliflozin 100 mg group and 8 subjects in canagliflozin 300 mg group had events considered by the investigator to be severe in intensity; all other subjects had events that were mild or moderate in severity. There was a low incidence of discontinuations due to this adverse event.

Table 18: Overall Summary of Osmotic Diuresis-related Adverse Events in the Broad Dataset (through 01 July 2012)

	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)	All CANA Minus -- All Non-CANA - Diff(%)	95%CI[a]
Total no. subjects with osmotic diuresis-related adverse events	79 (2.4)	227 (7.3)	243 (7.9)	470 (7.6)	5.2	(4.3; 6.1)
Incidence rate per 1000 subject-years exposure	*19.63*	*55.70*	*60.95*	*58.29*		
Grouped Terms:						
Polyuria/Pollakiuria	64 (2.0)	188 (6.1)	193 (6.3)	381 (6.2)	4.2	(3.4; 5.0)
Thirst	18 (0.6)	85 (2.7)	87 (2.8)	172 (2.8)	2.2	(1.7; 2.7)
Adverse event leading to discontinuation	2 (0.1)	8 (0.3)	9 (0.3)	17 (0.3)	0.2	(0.0; 0.4)
Serious adverse event	0	0	0	0		

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

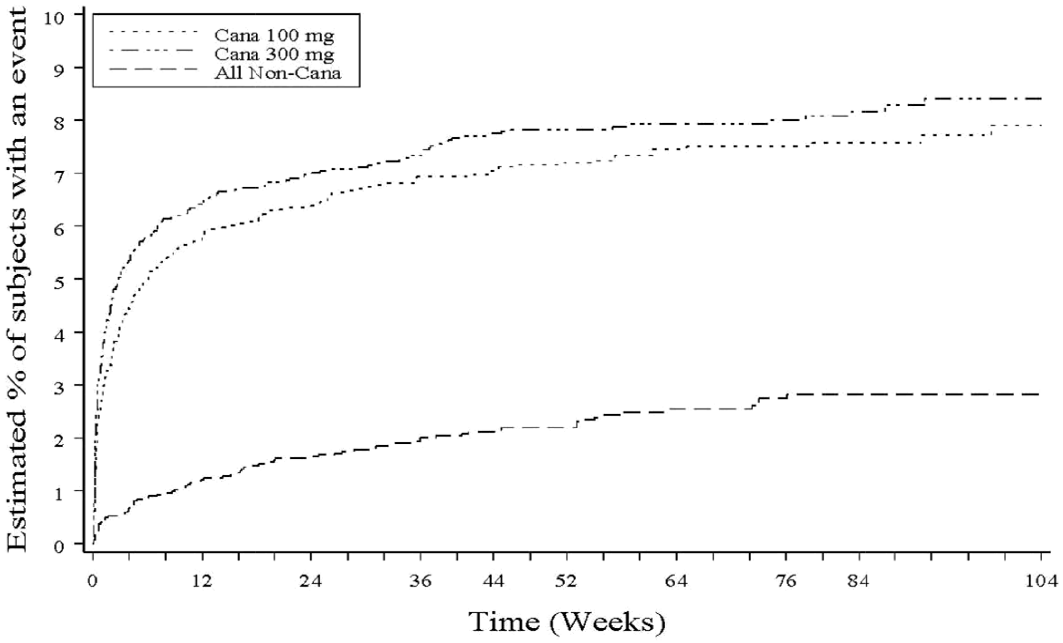
Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.

Note: Exposure adjusted incidence rates are per 1000 subject-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total subject-year exposure for all safety subjects in each treatment group).

Cross-reference: tae69osmo0401jul12rae2osmoticci.rtf generated by rae2osmoticci.sas, 04DEC2012 10:09

In both canagliflozin treatment groups, the majority of osmotic diuresis-related adverse events occurred within the first 6 weeks of the start of treatment, as indicated by Kaplan-Meier estimates of time to onset of the first event (Figure 25).

Figure 25: Kaplan-Meier Plot of Time to the First Osmotic Diuresis-related Adverse Event in the Broad Dataset (through 01 July 2012)



No. of Subjects										
Cana 100 mg	3092	2810	2656	2532	2459	2412	1673	1332	1016	348
Cana 300 mg	3085	2749	2586	2471	2398	2351	1603	1294	979	347
All Non-Cana	3262	3082	2848	2672	2573	2502	1634	1299	994	347

Pooled Renal Impairment Dataset

In the Renal Impairment Dataset, the incidence of osmotic diuresis-related adverse events was only modestly higher with canagliflozin, with one or more of the osmotic diuresis-related events reported in 4.1% and 3.8% in the canagliflozin 100 mg and 300 mg groups, respectively, and 3.7% of the placebo group, with no events leading to discontinuation or serious adverse events.

6.3.4.3. Summary

A non-dose-related higher incidence of adverse events related to osmotic diuresis (events reflecting increased frequency or urine volume and reflecting increase in fluid intake or thirst) was observed with canagliflozin treatment. These events tended to occur early after initiation of canagliflozin treatment, were considered mild or moderate in intensity, and infrequently led to discontinuation from the study.

6.3.5. Adverse Events Related to Reduced Intravascular Volume

6.3.5.1. Introduction and Data Analysis

In order to fully evaluate adverse events related to reduced intravascular volume, a pre-specified query including a list of adverse event preferred terms potentially reflecting reduced intravascular volume was applied so as to better characterize the overall incidence and profile (eg, onset, intensity, discontinuation rate) of such adverse events. These potentially associated

terms were grouped for analysis. The following list of preferred terms were included: BP decreased, dehydration, diastolic hypotension, dizziness postural, hypotension, hypovolemia, hypovolemic shock, orthostatic BP decreased, orthostatic hypotension, orthostatic intolerance, postural orthostatic tachycardia syndrome, presyncope, shock, syncope, and urine output decreased. From this list, the following terms were reported in the Phase 3 database: BP decreased, dehydration, dizziness postural, hypotension, orthostatic hypotension, orthostatic intolerance, presyncope, and syncope. Note that these terms are based upon investigator assessment and adverse event terms as reported by the investigator. The adverse event of dizziness was not included, as this is often less specific and can reflect other processes, but was examined in each study and pooled population.

6.3.5.2. Incidence and Characteristics of Adverse Events Related to Reduced Intravascular Volume

Broad Dataset

The incidence in the Broad Dataset (results through 01 July 2012) is presented in Table 19. There was a dose-related higher incidence of adverse events related to reduced intravascular volume in the canagliflozin groups relative to the non-canagliflozin group. There was no notable increase in the occurrence of serious adverse events or discontinuations due to adverse events of reduced intravascular volume in the canagliflozin groups relative to the non-canagliflozin group, and most adverse events were assessed by the investigator as mild or moderate in intensity.

Table 19: Overall Summary of Reduced Intravascular Volume-related Adverse Events in Broad Dataset (through 01 July 2012)

Number (%) of subjects with at least one reduced intravascular volume-related adverse event of following types:	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)	All CANA Minus -- All Non-CANA - Diff(%)	95%CI[a]
Any adverse event[b]	78 (2.4)	99 (3.2)	141 (4.6)	240 (3.9)	1.5	(0.8; 2.2)
Incidence rate per 1000 subject-years exposure	*19.38*	*24.29*	*35.36*	*29.77*		
Adverse event[b] leading to discontinuation	4 (0.1)	2 (0.1)	3 (0.1)	5 (0.1)	-0.0	(-0.2; 0.1)
Adverse event[b] related to study drug[c]	16 (0.5)	25 (0.8)	51 (1.7)	76 (1.2)	0.7	(0.4; 1.1)
Serious adverse event	11 (0.3)	12 (0.4)	8 (0.3)	20 (0.3)	-0.0	(-0.3; 0.3)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.
[b] Adverse events based upon a prespecified list of preferred terms from a MedDRA query listed in the Statistical Analysis Plan (SAP).
[c] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.
Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.
Note: Exposure adjusted incidence rates are per 1000 subject-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total subject-year exposure for all safety subjects in each treatment group).
Cross-reference: tae45b0401jul12raevol1ci.rtf generated by raevol1ci.sas, 11DEC2012 11:30

Specific adverse events related to reduced intravascular volume are presented in Table 20.

Table 20: Specific Reduced Intravascular Volume-related Adverse Events in Broad Dataset (through 01 July 2012)

Dictionary-Derived Term	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)
Total no. subjects with adverse events[a]	78 (2.4)	99 (3.2)	141 (4.6)	240 (3.9)
Specific Adverse Events:				
Blood pressure decreased	1 (<0.1)	2 (0.1)	2 (0.1)	4 (0.1)
Blood pressure orthostatic decreased	0	1 (<0.1)	0	1 (<0.1)
Dehydration	13 (0.4)	6 (0.2)	13 (0.4)	19 (0.3)
Dizziness postural	24 (0.7)	26 (0.8)	33 (1.1)	59 (1.0)
Hypotension	20 (0.6)	47 (1.5)	60 (1.9)	107 (1.7)
Hypovolaemia	1 (<0.1)	0	0	0
Hypovolaemic shock	0	0	1 (<0.1)	1 (<0.1)
Orthostatic hypotension	6 (0.2)	8 (0.3)	27 (0.9)	35 (0.6)
Orthostatic intolerance	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Presyncope	9 (0.3)	4 (0.1)	3 (0.1)	7 (0.1)
Syncope	13 (0.4)	12 (0.4)	20 (0.6)	32 (0.5)
Urine output decreased	1 (<0.1)	0	0	0

[a] Adverse events based upon a prespecified list of preferred terms from a MedDRA query listed in the Statistical Analysis Plan (SAP).

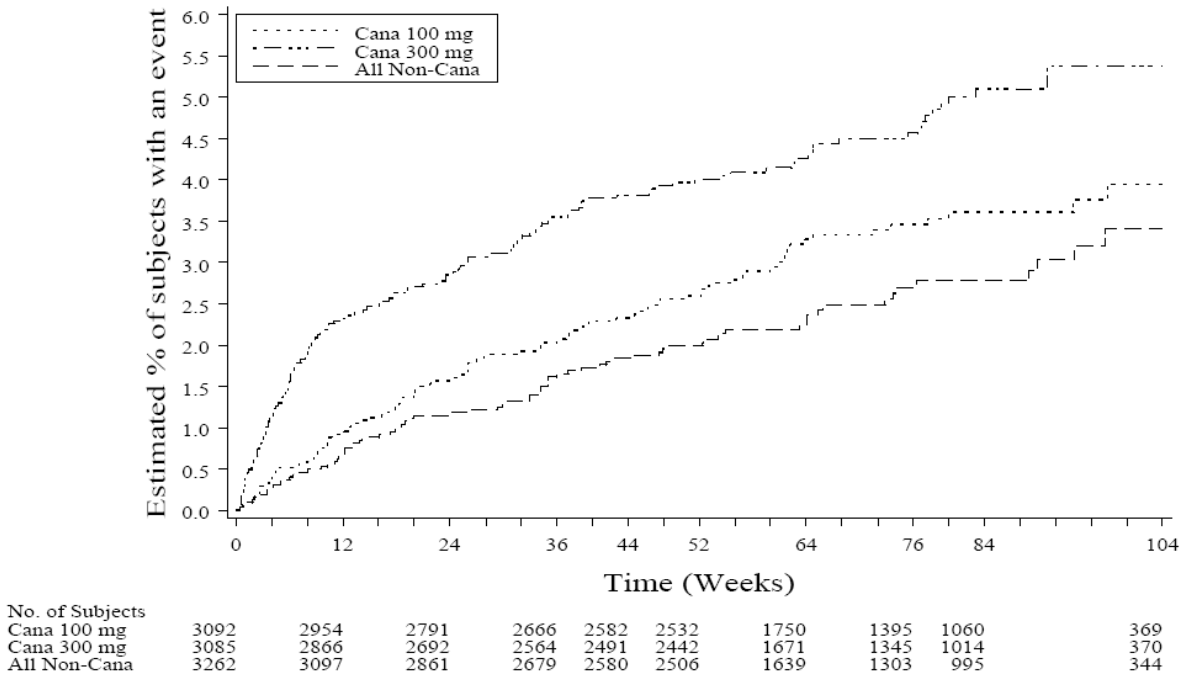
Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events

Cross-reference: tae45vd0401jul12raevol2.rtf generated by raevol2.sas, 11DEC2012 11:24

An additional analysis was conducted to assess changes in medical management in subjects with a reduced intravascular volume-related adverse event. This analysis showed that approximately two-thirds of subjects with a reduced intravascular volume-related event had a modification (generally an interruption or dose reduction) of BP-lowering medications (including diuretics) over a 60-day time period after the onset of the adverse event.

Adverse events related to reduced intravascular volume in the canagliflozin 300 mg group tended to occur earlier, as shown in the Kaplan-Meier plot of time to onset of the first event (Figure 26), with most events having been observed within the first 12 weeks after initiation of treatment, and no further increment in events in the canagliflozin relative to the non-canagliflozin group after about 26 weeks.

Figure 26: Kaplan-Meier Plot of Time to the First Reduced Intravascular Volume-related Adverse Event in Broad Dataset (through 01 July 2012)



Pooled Renal Impairment Dataset

In the Pooled Renal Impairment Dataset, the incidence of reduced intravascular volume-related adverse events was higher in the combined canagliflozin group (7.0%) compared with the placebo group (2.9%) (Table 21). The incidence was higher in the canagliflozin 300 mg group (8.5%) compared with the canagliflozin 100 mg group (5.3%). Reduced intravascular volume-related adverse events were serious in 4 (0.6%) subjects in the combined canagliflozin group and 5 (1.3%) subjects in the placebo group, and led to discontinuation in 3 (0.4%) subjects in the canagliflozin groups and no subjects in the placebo group.

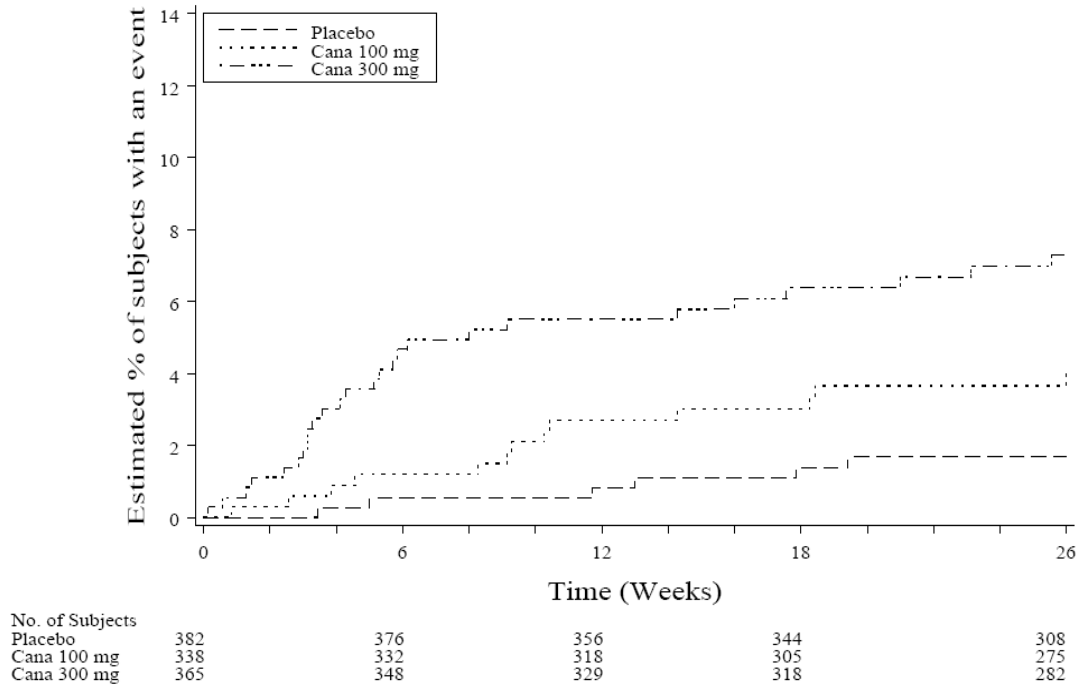
Table 21: Overall Summary of Reduced Intravascular Volume-related Adverse Events in Renal Impairment Dataset

Number (%) of subjects with at least one reduced intravascular volume-related adverse event of following types:	Placebo (N=382) n (%)	CANA 100 mg (N=338) n (%)	CANA 300 mg (N=365) n (%)	All CANA (N=703) n (%)	All CANA Minus ---- Placebo ---- Diff(%)	95%CI[a]
Any adverse event[b]	11 (2.9)	18 (5.3)	31 (8.5)	49 (7.0)	4.1	(1.4; 6.8)
Adverse event[b] leading to discontinuation	0	1 (0.3)	2 (0.5)	3 (0.4)	0.4	(-0.3; 1.1)
Adverse event[b] related to study drug[c]	3 (0.8)	8 (2.4)	11 (3.0)	19 (2.7)	1.9	(0.2; 3.6)
Serious adverse event	5 (1.3)	1 (0.3)	3 (0.8)	4 (0.6)	-0.7	(-2.2; 0.7)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.
[b] Reduced intravascular volume-related adverse events based upon a prespecified list of preferred terms from a MedDRA query listed in the SAP
[c] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.
Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication
Cross-reference: tae45b02raevol1ci_02.rtf generated by raevol1ci_02.sas, 11DEC2012 13:05

Consistent with the Broad Dataset, the most common reduced intravascular volume-related adverse event terms in the combined canagliflozin group were hypotension (21 [3.0%] subjects in the combined canagliflozin group and 3 [0.8%] subjects in the placebo group) and dizziness postural (14 [2.0%] subjects in the combined canagliflozin group and 2 [0.5%] subjects in the placebo group). The incidence of syncope and presyncope was low and similar in all groups. The time course of onset of the events in this dataset was similar to that observed in the Broad Dataset (Figure 27).

Figure 27: Kaplan-Meier Plot of Time To the First Reduced Intravascular Volume-related Adverse Event in the Renal Impairment Dataset



In the Placebo-controlled Studies Dataset, the occurrence of reduced intravascular volume-related adverse events was only slightly increased in the canagliflozin groups: the incidence of such adverse events was 1.2% and 1.3% in the canagliflozin 100 mg and 300 mg groups, respectively, compared with 1.1% in the placebo group, and no serious adverse events or events leading to discontinuation were reported with canagliflozin treatment in this dataset.

6.3.5.2.1. Risk Factors Analysis

To understand risk factors for adverse events related to reduced intravascular volume, a series of subgroup analyses were conducted in the Broad Dataset. Several factors leading to a more prominent dose-related increased rate of adverse events related to reduced intravascular volume

were identified (Table 22), including age ≥75 years, use of loop diuretics, and lower eGFR (<60 mL/min/1.73 m^2). Across the subgroups with one of these 3 factors, the incidence of adverse events of reduced intravascular volume was above 8% in the canagliflozin 300 mg group, and ranged from 3% to >5% higher than in the canagliflozin 100 mg group. Other risk factors examined led to smaller dose-related increases (and generally ≤2% difference between canagliflozin groups). This information was used for proposed labeling, which recommends that canagliflozin 100 mg be the initial dose used in patients with one or more of these risk factors. The proposed labeling will also indicate that canagliflozin has diuretic action (as an osmotic diuretic) so that patients with dehydration should have this addressed prior to initiating canagliflozin treatment.

Table 22: Number of Subjects With Reduced Intravascular Volume-related Adverse Events by Selected Baseline Characteristics in the Broad Dataset – Core

	% (n) in population[a]	Incidence[b]			
		All Non-CANA % (n/N)	CANA 100 mg % (n/N)	CANA 300 mg % (n/N)	All CANA % (n/N)
eGFR (mL/min/1.73 m^2)	N = 9432				
<60	13.0% (n=1223)	2.5% (11/436)	4.7% (18/382)	8.1% (33/405)	6.5% (51/787)
60 to <90	54.6% (n=5154)	1.5% (26/1788)	2.4% (40/1686)	2.9% (48/1680)	2.6% (88/3366)
≥90	32.4% (n=3055)	1.2% (12/1035)	1.3% (13/1021)	2.4% (24/999)	1.8% (37/2020)
Age (years)	N=9439				
<75	94.8%(n= 8949)	1.4% (45/3107)	2.2% (63/2929)	3.1% (90/2913)	2.6%(153/5842)
≥75	51.9% (n=490)	2.6% (4/155)	4.9% (8/163)	8.7% (15/172)	6.9% (23/335)
Use of Loop Diuretics	N = 9439				
No	92.4% (n=8717)	1.2% (37/3006)	2.2% (64/2876)	2.9% (83/2835)	2.6% (147/5711)
Yes	7.6% (n=722)	4.7% (12/256)	3.2% (7/216)	8.8% (22/250)	6.2% (29/466)
Age <75, not on Loop Diuretics, and eGFR ≥60mL/min/1.73 m^2 (ie, none of the identified risk factors)	N = 9439 79.8% (n=7529)	1.1% (29/2604)	1.8% (45/2491)	2.2% (54/2434)	2.0% (99/4925)

[a] Number of subjects in the Safety analysis set with the baseline characteristic.
[b] Adverse events based upon a prespecified list of preferred terms from a MedDRA query listed in the SAP.
[c] Includes both loop and non-loop diuretics.
Cross-reference: Integrated Summary of Safety (ISS) attachments DAE70VDEGFR_03, DAE70VDSEX_03, DAE70VDAGE_03, DAE70VDHBA1C_03, DAE70VDACE_03, DAE70VDDIUR_03, DAE70VDLOOP_03, DAE70VDACEDIUR1_03, DAE70VDACEDIUR2_03, DAE70VDACEDIUR3_03, DAE70VDACEDIUR4_03,DAE70VDDIAB_03, DAE70VDCOMP_03, DAE70VDSBP_03, and DAE70VDAGE75_03, Table DAE32c_VDAC_03:

6.3.5.2.2. Summary

In summary, a dose-related increase in adverse events related to reduced intravascular volume was observed with canagliflozin treatment in the Broad Dataset and in the Renal Impairment Dataset, with only a minimal increase observed in the Placebo-controlled Studies Dataset. It is important to note that the higher incidence with canagliflozin treatment was seen in events of mild to moderate intensity and that canagliflozin treatment was not associated with an increase in serious adverse events related to reduced intravascular volume. The difference between the observations in the Placebo-controlled Studies Dataset and the Broad Dataset is likely related to the inclusion of more vulnerable subjects (such as the CANVAS [DIA3008] cardiac safety study

population) in the Broad Dataset. Risk factors for these reduced intravascular volume-related adverse events have been identified, including age ≥75 years, eGFR <60 mL/min/1.73 m^2, and use of loop diuretics. These events did not generally require discontinuation, but often required adjustment of concomitant blood-pressure lowering medications. Thus, these events were mild to moderate in intensity, and given the low occurrence of discontinuations due to these adverse events, were manageable. Risk factors associated with a higher incidence of these adverse effects are identified in the proposed label and the 100 mg dose will be recommended as the initial dose in patients with one or more of these factors.

6.3.6. Other Adverse Events Assessed as Adverse Drug Reactions

In the Placebo-controlled Studies Dataset, the incidence of the adverse event of constipation was higher in the combined canagliflozin group (2.0%, 34 subjects), without dose relationship, compared with the non-canagliflozin group (0.9%, 6 subjects). Events of constipation were mild or moderate in severity with only one event reported as serious and one event leading to discontinuation. An increase in incidence was also observed in the Broad Dataset (results through 01 July 2012), 3.1% and 3.0% in the canagliflozin 100 mg and 300 mg groups, respectively, and 2.4% in the non-canagliflozin group. With the association of constipation with diuretic agents, this adverse event was assessed as an ADR for canagliflozin.

Based upon the sponsor's review of adverse event incidences and patterns across the pooled databases, rash, and urticaria were assessed as ADRs. A slightly higher incidence of the adverse event of rash was reported, with the incidence in the Broad Dataset (results through 01 July 2012) in the combined canagliflozin group of 1.6% compared with 1.3% in the non-canagliflozin group subjects. No events consistent with Stevens-Johnson Syndrome were reported. Adverse event of urticaria were reported with a slightly higher incidence (0.4%) in the combined canagliflozin group relative to the non-canagliflozin group (0.3%). The majority of the events of urticaria were considered resolved while subjects continued taking study drug. No adverse events of urticaria were reported with respiratory symptoms or anaphylaxis.

6.4. Changes in Measures of Renal Function

6.4.1. Introduction and Overview

The increase in UGE induced by SGLT2 inhibition leads to an osmotic diuresis, with the potential for a reduction in eGFR due to the reduced intravascular volume with reduced renal perfusion (ie, a pre-renal pattern). In Phase 1 studies, variable modest and reversible rises in blood urea nitrogen and creatinine were observed.

In the Phase 2b study in subjects with T2DM (DIA2001), serum creatinine increased slightly (approximately by 0.1 mg/dL), but returned to baseline levels, similar to placebo, across the canagliflozin groups by Week 12 (the last visit of the double-blind treatment period). A detailed assessment of renal function changes and adverse events with canagliflozin treatment was conducted in Phase 3 studies because of the renal target for the mechanism of action of canagliflozin and the potential for changes in intravascular volume to impact renal function.

Note that in the canagliflozin Phase 3 program, eGFR was determined using the Modification of Diet in Renal Disease (MDRD) equation. The rationale for using this approach was based upon validation and accuracy of this equation in patients with chronic kidney disease and diabetes (Levey 1999, Rigalleau 2005), broad use in clinical practice, and avoidance of overestimating eGFR in obese subjects compared to another commonly-used eGFR equation (ie, Cockcroft-Gault) which uses body weight to determine eGFR.

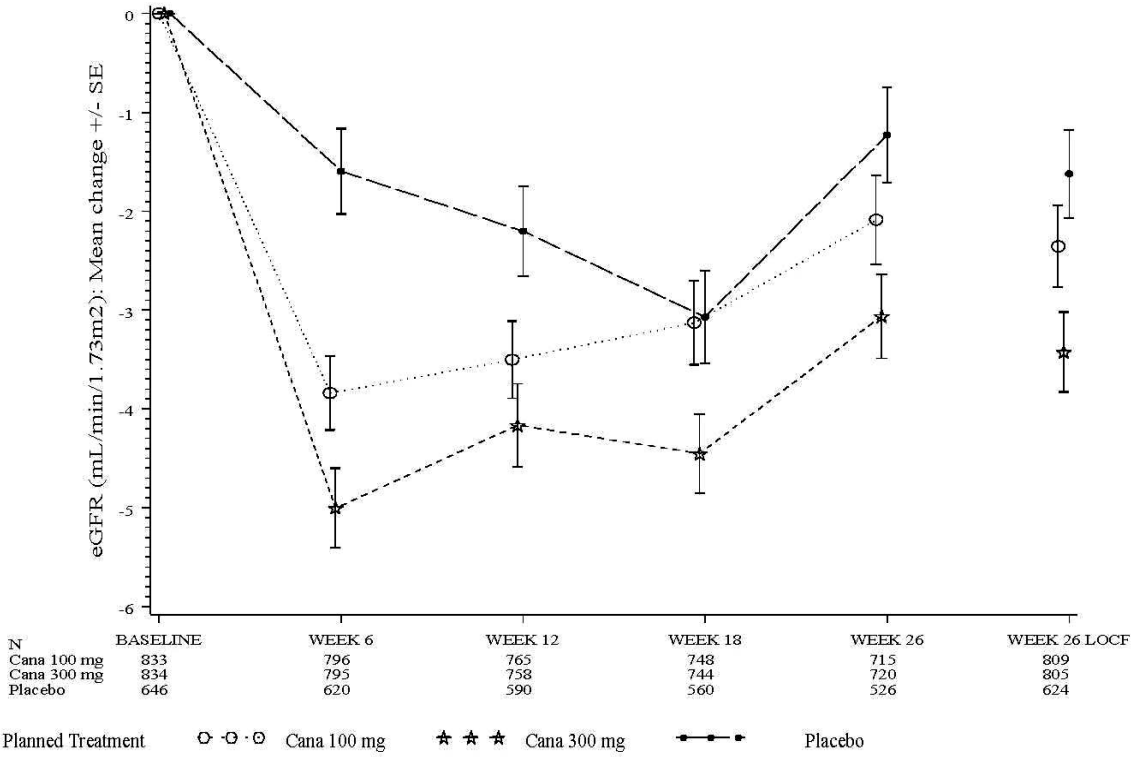
The section below reviews renal-related laboratory changes (mean changes over time for renal function tests and outlier analyses based upon prespecified change criteria), renal-related adverse events, and results of adjudication on renal events meeting pre-specified criteria.

6.4.2. Mean Changes and Outlier Analyses of Changes in eGFR

6.4.2.1. Mean Changes in eGFR

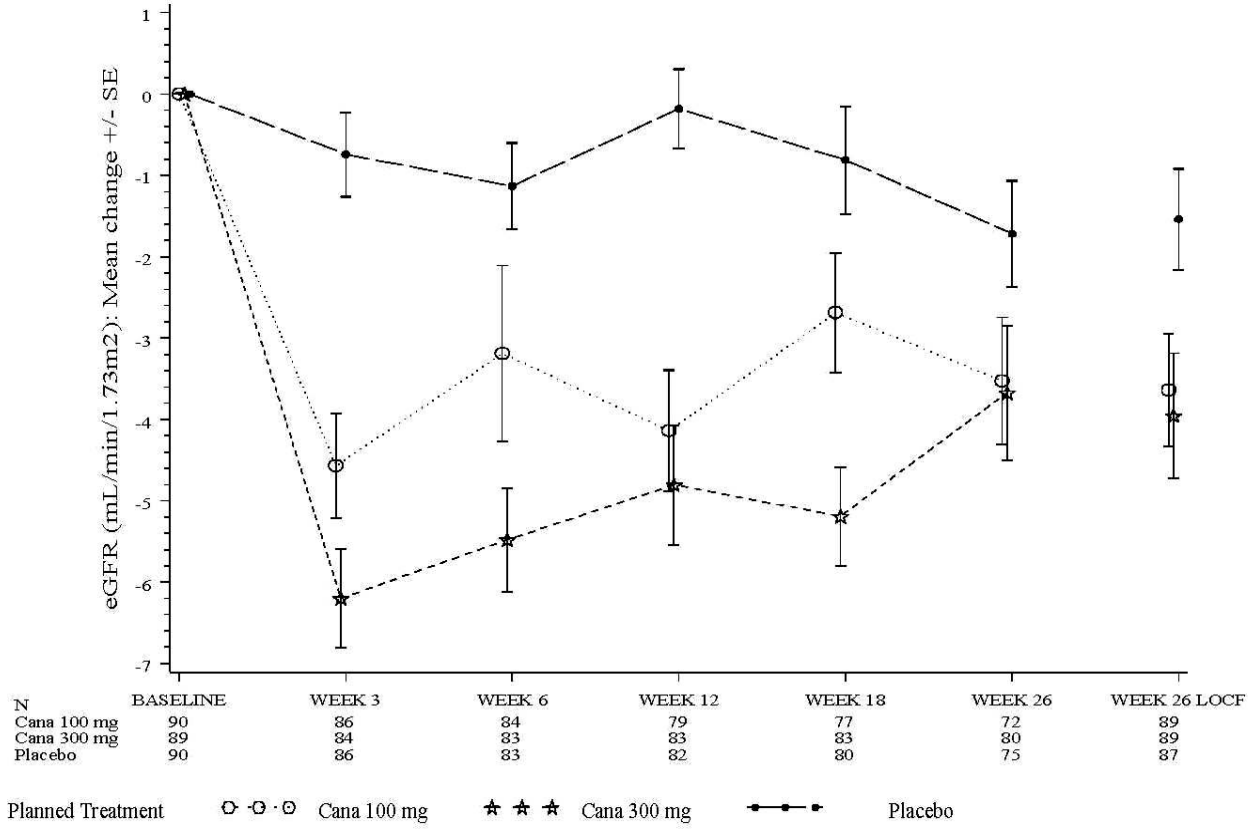
Mean changes over time are presented below for the 26-week results from the Placebo-controlled Studies Dataset (note: mean changes are provided in this dataset, since visit schedules and study durations differed across the Broad Dataset, limiting analyses of mean changes over time) and Study DIA3004 (dedicated study in subjects with renal impairment). In addition, to provide mean changes over a longer time period, 52-week results from the active-comparator (glimepiride) controlled add-on to metformin study (DIA3009) are also presented. In the Placebo-controlled Studies Dataset, as shown in Figure 28, an initial mean decrease from baseline (with mean baseline of 88 mL/min/1.73 m^2) in eGFR was observed in all treatment groups, more prominently in both canagliflozin groups, with the nadir observed by Week 6, with subsequent increases at Week 26 from the nadir value. At Week 26, mean percent changes from baseline of -1.8% and -3.0% were seen in the canagliflozin 100 mg and 300 mg groups, respectively, and -0.5% in the placebo group.

Figure 28: Mean Change (+/-SE) in eGFR (mL/min/1.73 m^2) From Baseline Over Time in Placebo-controlled Studies Dataset



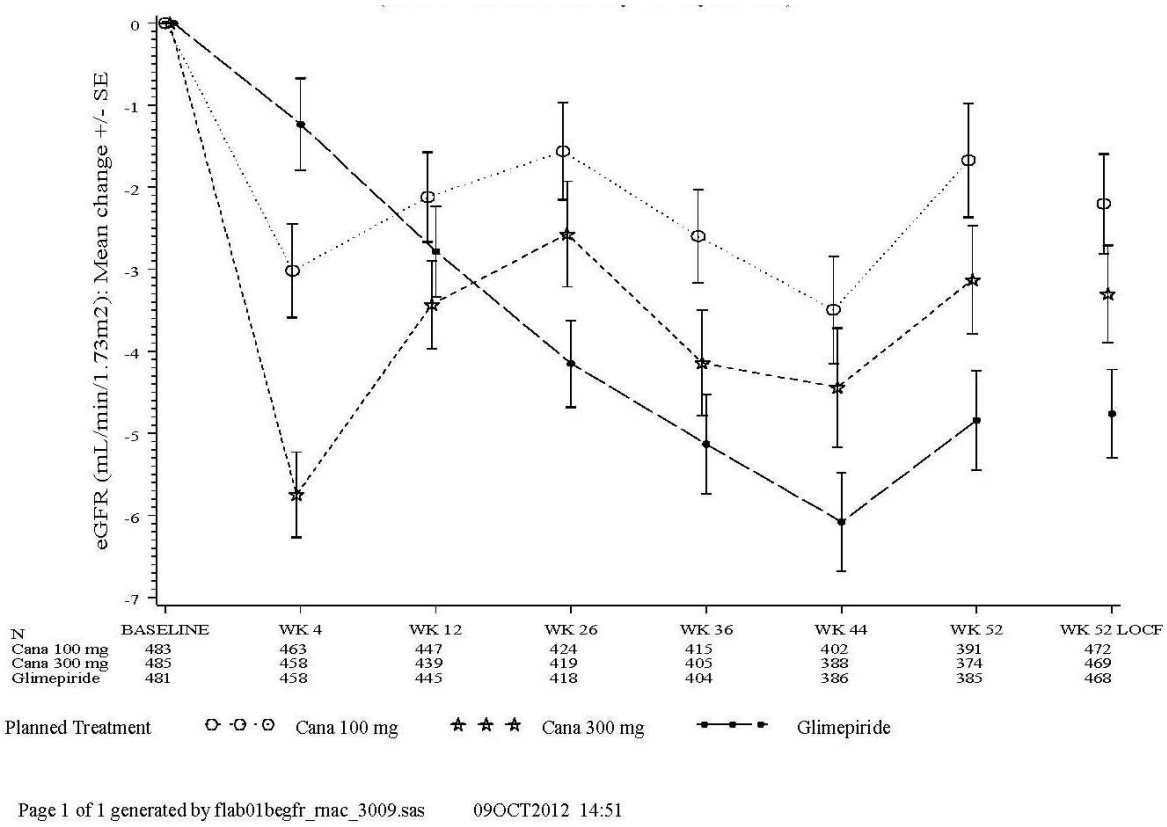
As seen in Figure 29, in the study in subjects with renal impairment (DIA3004), with mean baseline eGFR 39.4 mL/min/1.73 m^2, the absolute decreases in eGFR were similar as observed in the Placebo-controlled Studies Dataset described above; however, with the lower baseline eGFR, larger decreases in percent mean change from baseline were observed Week 26 (-8.3% and -8.9%, respectively, in the canagliflozin 100 mg and 300 mg groups, with a change from baseline in the placebo group of -3.8%). The decrease in eGFR was largest at the initial postbaseline study visit (Week 3) and trended towards baseline over the subsequent treatment period (with a between-group change from baseline difference relative to placebo in eGFR of <3 mL/min/1.73 m^2 at Week 26). An LOCF analysis was also conducted for eGFR to assure that subjects discontinuing prior to Week 26 would not confound the over time analysis of this endpoint. The LOCF analysis and the over time analysis (which does not carry forward results) were not discernibly different.

Figure 29: Mean Change From Baseline Over Time in eGFR in Study in Subjects with Renal Impairment (Study DIA3004)



In the 52-week active-comparator (glimepiride) controlled add-on to metformin study (DIA3009) study, as shown in Figure 30, there were small mean decreases in eGFR from baseline (mean baseline value of 90.2 mL/min/1.73 m^2) through Week 52 in all treatment groups, with the largest decrease observed in the glimepiride group. After an initial decrease observed in both canagliflozin groups, eGFR remained, with some variability, generally stable.

Figure 30: Mean Percent Change (+/-SE) in eGFR From Baseline Over Time (Study DIA3009)



6.4.2.2. Mean Changes After Discontinuation of Study Drug

6.4.2.2.1. Phase 2 Studies

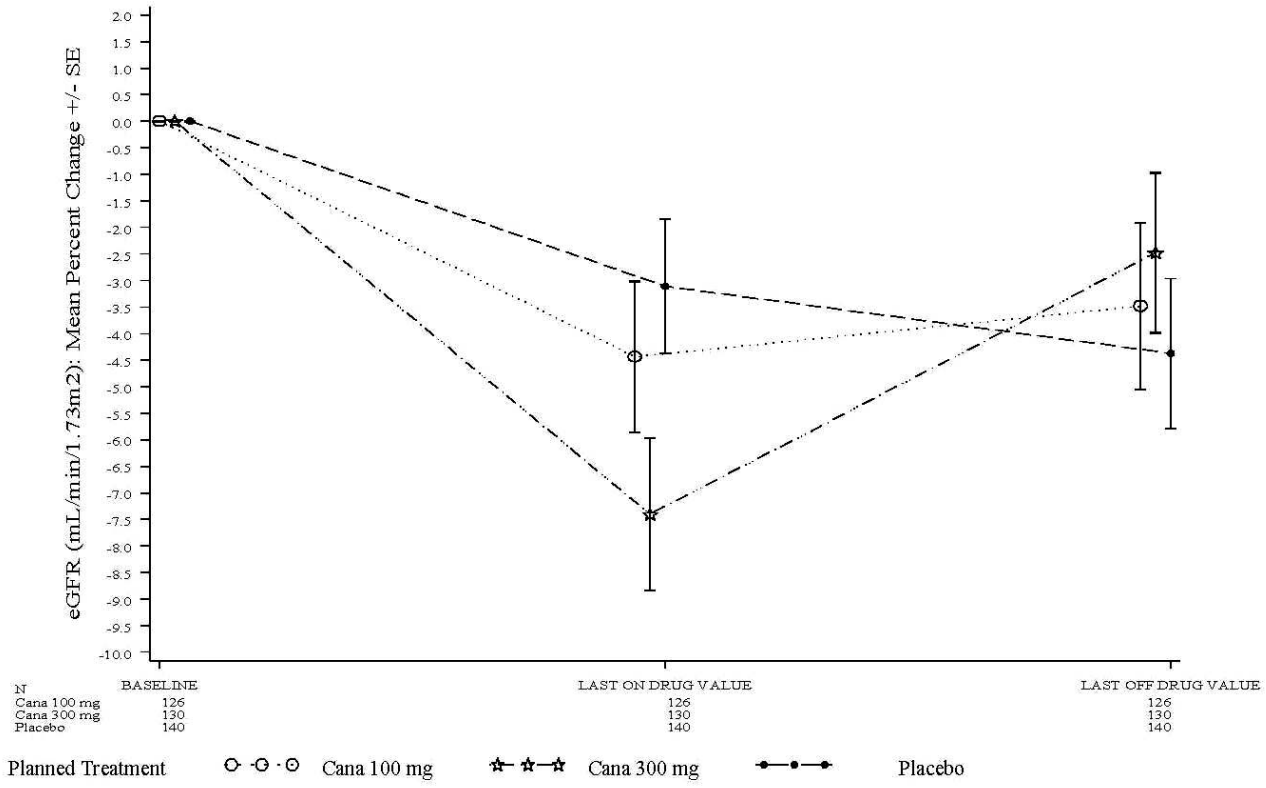
The 12-week non-diabetic overweight/obese Phase 2 study, OBE2001, in which 50-, 100-, and 300 mg qd dosing was examined, included assessments of laboratory values 2 weeks after discontinuation of study drug. In this study, the eGFR decreased slightly from baseline at Week 12 in the canagliflozin 50 and 100 mg groups (-1.0 and -1.8 mL/min/1.73 m^2, respectively) compared with placebo (0.3 mL/min/1.73 m^2); a reduction in eGFR was not apparent in the canagliflozin 300 mg qd dose group. Values returned to baseline levels at the follow-up visit approximately 2 weeks after the scheduled discontinuation of study drug. In the 12-week Phase 2b study in subjects with T2DM, no post-double-blind period laboratory studies were collected; however, in this study, as noted in Section 6.4.1, a small increase in serum creatinine was seen (approximately 0.1 mg/dL maximal increase across canagliflozin groups) at Week 2, and subsequently decreased so that serum creatinine was similar to the placebo group and to baseline at Week 12.

6.4.2.2.2. Phase 3 Study: DIA3008 (CV Safety Study)

Follow-up blood chemistry studies were not routinely performed in the Phase 3 program; however, in DIA3008, central laboratory assessments were performed at follow-up visits after discontinuation from study drug. Baseline characteristics for the 396 subjects discontinued, and who had follow-up laboratory results were generally similar to the overall study population

(median age 64.0 years, 66.7% male, and 72% white, median eGFR 77 mL/min/1.73 m^2). The median duration from Day 1 to the last on-drug eGFR value was 184 days in the canagliflozin 100 mg group, 128 days in the canagliflozin 300 mg group, and 130 days in the placebo group. The median duration from the last dose of study drug to the last off-drug eGFR value was similar across treatment groups: 66 and 61 days in the canagliflozin 100 and 300 mg groups, respectively, and 68 days in the placebo group. As shown in Figure 31, after discontinuation of study drug, eGFR values in both canagliflozin groups increased to values only slightly lower than baseline levels, while in the placebo group, a small further decline is observed such that there was no meaningful difference across groups for percent change from baseline in eGFR at follow-up. For the subset of 47 subjects in the combined canagliflozin groups with baseline lower eGFR values (eGFR ≥30 and <60 mL/min/1.73 m^2) who discontinued and had a post discontinuation eGFR measurement, a similar pattern was observed, with the follow-up eGFR percent change from baseline value in the canagliflozin groups similar to the eGFR percent change from baseline value in the placebo group.

Figure 31: Mean Percent Change (+/-SE) in eGFR for Subjects Who Discontinued and Have a Posttreatment Value (>5 Days After the Last Study Medication) Study DIA3008



Note: Safety analysis set

6.4.2.3. Outlier Analysis: Subjects Meeting Specific Criteria for Reductions in eGFR

To assess potentially clinically important changes in renal function, a standardized approach was implemented, assessing the proportion of subjects meeting 1 or both of the following eGFR change criteria: >30% reduction from baseline (and <80 mL/min/1.73 m^2) or >50% reduction from baseline. Assessments were conducted at 2 time points: proportion of subjects with changes in eGFR meeting the criteria at "any" postbaseline value (ie, any time during the double-blind treatment period) or at the "last" available value (while the subject was on study drug, defined as a measurement obtained not longer than 2 days after the last dose of study drug). The criteria were selected to be consistent with cutpoints used to assess important changes for ACE inhibitors (Bakris 2000) and also consistent with the Acute Kidney Injury Network for acute kidney injury Stage 1 (Englberger 2011).

Proportions of subjects meeting the eGFR change criteria for the Broad Dataset (results through 01 July 2012) and the Pooled Renal Impairment Dataset are presented below.

6.4.2.3.1. Phase 3 Results

6.4.2.3.1.1. Broad Dataset

In the Broad Dataset (results through 01 July 2012), the incidence of subjects meeting the eGFR specific change criterion of a decrease >30% from baseline (and <80 mL/min/1.73 m^2) and at any time during the double-blind treatment period was similar in the canagliflozin 100 mg (6.4%) and non-canagliflozin groups (6.2%) and higher in the canagliflozin 300 mg group (9.7%) (Table 23). The incidence of subjects whose last (ie, not longer than 2 days after last dose of study drug) postbaseline eGFR value met this criterion was lower, with 2.5% and 2.5% of subjects in the canagliflozin 100 mg and non-canagliflozin groups, respectively, and 3.6% in the canagliflozin 300 mg group. A time to event analysis showed that the largest increment in events meeting criteria in the canagliflozin 300 mg group was at Week 6, with no substantive further incremental differences across treatment groups. The small number of subjects with larger reductions in eGFR underwent adjudication (including of events with sustained or last value decreases in eGFR of >50% from baseline), see Section 6.4.2.6.

Table 23: Number of Subjects With eGFR Laboratory Values Meeting Specific Change Criteria in Broad Dataset (through 01 July 2012)

	All Non-CANA n (%)	CANA 100 mg n (%)	CANA 300 mg n (%)	All CANA n (%)	All CANA Minus -- All Non-CANA - 95%CI[a]
Serum eGFR (mL/min/1.73 m^2)					
Any postbaseline value	3162	3020	2971	5991	
eGFR <80 mL/min/1.73 m^2 and decrease >30% from baseline	195 (6.2)	193 (6.4)	288 (9.7)	481 (8.0)	(0.8; 3.0)
eGFR decrease > 50% from baseline	16 (0.5)	20 (0.7)	27 (0.9)	47 (0.8)	(-0.1; 0.6)
Last postbaseline value	3162	3020	2971	5991	
eGFR <80 mL/min/1.73 m^2 and decrease >30% from baseline	79 (2.5)	75 (2.5)	107 (3.6)	182 (3.0)	(-0.2; 1.3)
eGFR decrease >50% from baseline	6 (0.2)	3 (0.1)	9 (0.3)	12 (0.2)	(-0.2; 0.2)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.
Note: Percentages calculated with the number of subjects per time interval as denominator.
Cross-reference: 4MSU Table 23; attachment DLAB02B_04_01JUL12

6.4.2.3.1.2. Pooled Renal Impairment Dataset

In the Pooled Renal Impairment Dataset, the incidence of subjects who met the eGFR change criterion of a decrease >30% from baseline (and <80 mL/min/1.73 m^2) for "any" postbaseline value was higher in the canagliflozin 100 mg and 300 mg groups (9.3% and 12.2%, respectively) compared with the placebo group (4.9%) (Table 24). In contrast, the incidence of subjects meeting this eGFR change criterion at the last on-study drug value was similar in the canagliflozin 100 mg and placebo groups, and only slightly higher in the canagliflozin 300 mg group.

The incidence of subjects with any postbaseline eGFR value with a decrease of >50% from baseline was generally low but higher in the canagliflozin 100 mg and 300 mg groups (5 [1.5%] subjects and 3 [0.9%] subjects, respectively) compared with no subjects in the placebo group (Table 24). Only 1 subject in the canagliflozin 100 mg group had a "last" postbaseline eGFR value that was decreased >50% from baseline. This subject's event was adjudicated as possibly related to study drug, and is discussed in Section 6.4.2.6.

Table 24: Number of Subjects With eGFR Values Outside Pre-Defined Limits in the Pooled Renal Impairment Dataset

	Placebo n (%)	CANA 100 mg n (%)	CANA 300 mg n (%)	All CANA n (%)	All CANA Minus ---- Placebo ---- 95%CI[a]
Serum eGFR (mL/min/1.73 m^2)					
Any postbaseline value	367	332	352	684	
eGFR <80 mL/min/1.73 m^2 and decrease >30% from baseline	18 (4.9)	31 (9.3)	43 (12.2)	74 (10.8)	(2.5; 9.3)
eGFR decrease > 50% from baseline	0	5 (1.5)	3 (0.9)	8 (1.2)	(0.2; 2.2)
Last postbaseline value	367	332	352	684	
eGFR <80 mL/min/1.73 m^2 and decrease >30% from baseline	12 (3.3)	10 (3.0)	14 (4.0)	24 (3.5)	(-2.3; 2.7)
eGFR decrease >50% from baseline	0	1 (0.3)	0	1 (0.1)	

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.
Note: Percentages calculated with the number of subjects per time interval as denominator.
Cross-reference: DLAB02B_02

6.4.2.4. Renal Safety Biomarkers

6.4.2.4.1. Biomarkers in Phase 2 Studies

In the Phase 2 studies in T2DM and non-diabetic obese subjects, no discernible changes were seen by the Week 12/end-of-treatment visit in indicators of proximal tubular function. With canagliflozin treatment, urinary phosphate, urinary phosphate/creatinine ratio, urinary beta-2-microglobulin, urinary beta-2-microglobulin/creatinine, serum 1,25-dihydroxyvitamin D, and acid-base balance were not substantively changed relative to placebo, with reductions in the urinary albumin/creatinine ratio (ACR). In both studies, urinary N-acetyl-beta-D-glucosaminidase (NAG) and the NAG/creatinine ratio were modestly increased at Week 3 in the canagliflozin groups (not dose dependent) compared with the placebo group, and waned, but remained elevated, with longer treatment duration; since increased UGE is associated with increased urinary NAG excretion (Brouhard 1984), this selective increase in urinary NAG excretion with canagliflozin, and not in other proximal tubular markers, is a non-specific finding.

6.4.2.4.2. Biomarker in Phase 3 Studies: Urinary Albumin to Creatinine Ratio (ACR)

The urinary ACR, an index reflecting either disordered glomerular and/or tubular function, was analyzed in 4 Phase 3 studies (DIA3004, DIA3005, DIA3008, and DIA3009); for all 4 studies, numerically greater mean and median reductions with both doses of canagliflozin relative to placebo or comparator were observed in the urinary ACR. Since the largest experience was from the DIA3008 study, these results are presented in this section.

In DIA3008, the ACR response was examined in subjects overall and in those subjects with normo-, micro-, or macro-albuminuria at baseline; in subjects with micro- and macro-albuminuria at baseline, substantive reductions with canagliflozin relative to placebo in urinary ACR were observed (Table 25). In subjects with normo-albuminuria, minimal increases

in ACR, that were smaller in the canagliflozin groups relative to the placebo group, were seen. In addition, progression of albuminuria (ie, from normo- to micro- or macro-, or from micro- to macroalbuminuria) was evaluated in study DIA3008. The data showed that a smaller proportion of subjects in the canagliflozin 100 mg and 300 mg groups relative to the placebo group progressed from a lower to a higher level of albuminuria at Week 52 (Table 26).

Table 25: Urine Albumin/Creatinine Ratio: Mean and Median Change from Baseline at Week 52 by Presence of Albuminuria at Baseline (DIA3008 Study)

Baseline Categories (by ACR)	Placebo	CANA 100 mg	CANA 300 mg	All CANA
Overall				
N	1331	1363	1332	2695
Mean baseline (µg/mg)	100.2	80.2	96.6	88.3
Mean change (SD)	26.3 (282.09)	-18.9 (220.47)	-32.8 (218.78)	-25.7 (219.71)
Median change	0.4	-0.3	-0.8	-0.5
Normo-albuminuria				
N	946	971	961	1932
Mean baseline (µg/mg)	10.2	10.1	9.8	9.9
Mean change (SD)	10.2 (56.45)	7.6 (63.38)	7.3 (74.91)	7.4 (69.28)
Median change	0.7	0.7	0.2	0.4
Micro-albuminuria				
N	289	320	288	608
Mean baseline (µg/mg)	90.0	92.7	104.5	98.3
Mean change (SD)	47.6 (204.79)	-8.0 (159.92)	-38.3 (104.33)	-22.1 (137.61)
Median change	-4.1	-24.2	-31.9	-26.8
Macro-albuminuria				
N	96	72	83	155
Mean baseline (µg/mg)	1018.8	970.6	1074.0	1026.0
Mean change (SD)	127.7 (979.49)	-416.7 (761.73)	-486.8 (672.32)	-453.4 (714.48)
Median change	-27.2	-306.5	-367.6	-327.9

Note: Within 2 days after last study medication
Cross-reference: tlab07dacr_rnac_4msu3008_rlbmc4msu3008.rtf generated by rlbmc4msu3008.sas, 02OCT2012 09:56,
tlab07aacr_rnac_4msu3008_rlbmc4msu3008.rtf generated by rlbmc4msu3008.sas, 27SEP2012 13:05,
tlab07bacr_rnac_4msu3008_rlbmc4msu3008.rtf generated by rlbmc4msu3008.sas, 27SEP2012 13:05

Table 26: Progression in Albuminuria: Proportion of Subjects Experiencing Progression From Baseline to Week 52 in Study DIA3008

	-- Placebo -		CANA 100 mg		CANA 300 mg		Pairwise Comparison CANA 100 mg vs Placebo		Pairwise Comparison CANA 300 mg versus Placebo	
	N	%	N	%	N	%	OR	95% CI [a]	OR	95% CI [a]
Urine albumin/creatinine (ug/mg)										
Progression	122	11.2	107	9.0	77	6.8	0.77	(0.59; 1.02)	0.57	(0.42; 0.77)
No progression	965	88.8	1077	91.0	1054	93.2				
Total	1087		1184		1131					

OR = Odds Ratio
[a] Pairwise comparison: CIs are based on the logistic regression model with treatment, stratification, and, Baseline ACR.
Note: Include only the subjects who had result of Albumin to Creatinine Ratio.
Cross-reference: tlab09acr_rnac_4msu3008_reff564msu3008.rtf generated by reff564msu3008.sas, 08OCT2012 16:27

6.4.2.5. Renal Adverse Events

In Phase 1 and 2 studies, there was no signal for an increase in renal-related adverse events; the experience in Phase 3 studies is summarized in the following section.

6.4.2.5.1. Data Analysis

To assure that all relevant renal-related adverse events would be reflected in the renal assessment, a standardized query was applied reflecting adverse events of reduced renal function either as a term captured in the acute renal failure Standard MedDRA Query (eg, renal impairment or renal failure) or as an adverse event in the Investigations SOC (ie, Blood creatinine increased, Glomerular filtration rate decreased), with grouped analysis of terms. This broad group of terms is referred to in this document as *renal-related adverse events*.

6.4.2.5.2. Phase 3 Results

6.4.2.5.2.1. Broad Dataset

The summary of renal-related adverse events in the Broad Dataset is shown in Table 27. The incidence of any renal-related adverse event was higher in the canagliflozin 100 mg group (3.1%) and the canagliflozin 300 mg group (3.6%) compared with the non-canagliflozin group (2.5%), with a similar incidence of adverse events leading to discontinuation in the canagliflozin 100 mg and non-canagliflozin groups, and a slightly higher incidence in the canagliflozin 300 mg group. The incidence of serious adverse events was similar in both canagliflozin groups relative to the non-canagliflozin group.

Table 27: Overall Summary of Renal-related Adverse Events in Broad Dataset (through 01 July 2012)

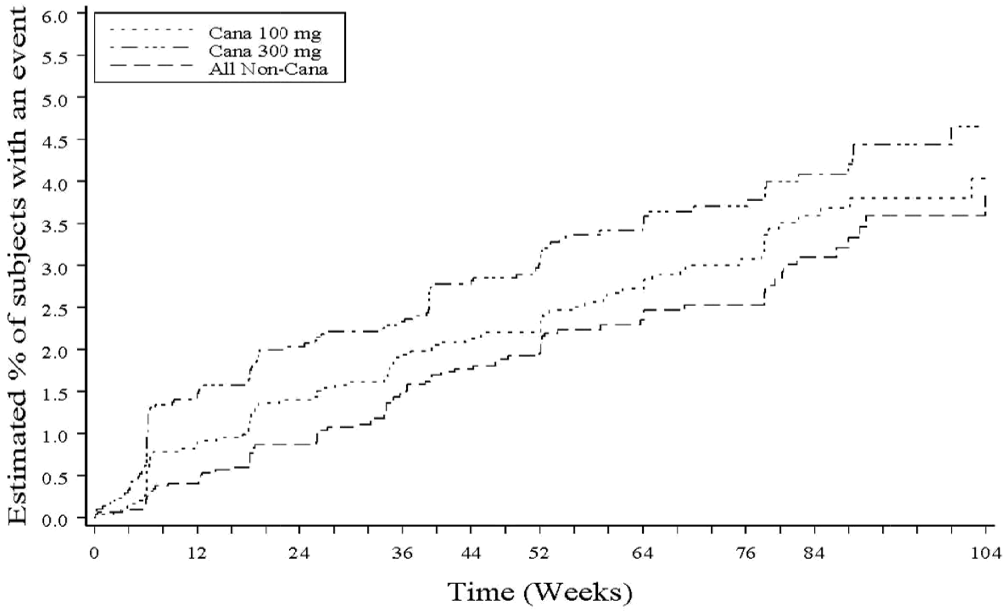
Number (%) of subjects with at least one renal-related adverse event of following types:	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)	All CANA Minus -- All Non-CANA - Diff(%)	95%CI[a]
Any adverse event[b]	82 (2.5)	96 (3.1)	111 (3.6)	207 (3.4)	0.8	(0.1; 1.6)
Incidence rate per 1000 subject-years exposure	*20.38*	*23.56*	*27.84*	*25.67*		
Adverse event[b] leading to discontinuation	17 (0.5)	16 (0.5)	34 (1.1)	50 (0.8)	0.3	(-0.1; 0.6)
Adverse event[b] related to study drug[c]	36 (1.1)	36 (1.2)	50 (1.6)	86 (1.4)	0.3	(-0.2; 0.8)
Serious adverse event	13 (0.4)	15 (0.5)	12 (0.4)	27 (0.4)	0.0	(-0.3; 0.3)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.
[b] Selected renal related adverse events include the prespecified list of acute renal failure preferred terms from a MedDRA query listed in the SAP and the additional preferred terms of Glomerular filtration rate decreased and Blood creatinine increased.
[c] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.
Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.
Note: Exposure adjusted incidence rates are per 1000 subject-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total subject-year exposure for all safety subjects in each treatment group).
Cross-reference: tae50bb0401jul12raeren1aci.rtf generated by raeren1aci.sas, 03DEC2012 09:53

The Kaplan-Meier curve for time to onset of selected renal-related adverse events in the Broad Dataset is presented in Figure 32. As seen in this figure, the increment in events occurred early, similar in timing to the occurrence of reduced intravascular volume-related adverse events (Figure 25), with no evident further incremental differences over time. The concurrence in time of onset of these adverse events and adverse events of reduced intravascular volume is consistent

with the anticipated mechanism of renal-related adverse events, related to hemodynamic changes with canagliflozin.

Figure 32: Kaplan-Meier Plot of Time Event for Renal-related Adverse Event in Broad Dataset (through 01 July 2012)



To examine outcomes in subjects discontinued due to renal-related adverse events, follow-up laboratory results were evaluated (from the central laboratory or reported in the database from local laboratory results). Among the 50 subjects in the canagliflozin groups discontinued due to renal-related adverse events, in 94% of subjects, posttreatment follow-up values were within 30% of the baseline value (50% were within 10%, and 84% were within 20%). The proportion of the 17 subjects in the non-canagliflozin group with resolution was similar, with 88% having posttreatment eGFR values within 30% of baseline at follow-up (25% within 10% and 63% within 20%). These results are similar to those observed for subjects meeting the change criteria for eGFR, with most subjects showing resolution or improvement, and a similar small proportion in the canagliflozin and non-canagliflozin groups showing persistent decreases in renal function.

6.4.2.5.2.2. Pooled Renal Impairment Dataset

The incidence of renal-related adverse events is shown in Table 28. The incidence of any renal-related adverse event was higher in the canagliflozin 100 mg and 300 mg groups compared the placebo group; however the incidence of events that led to discontinuation of study drug and events considered as drug-related was similar in the canagliflozin 100 mg and placebo groups, and only slightly higher in the canagliflozin 300 mg group relative to the other treatment groups. The incidence of serious adverse events was similar in all groups. This pattern, of an increase in renal-related adverse events overall with no notable increase in events leading to discontinuation

or of renal-related serious adverse events, is consistent with the pattern observed for events meeting criteria for decreases in eGFR (>30% reduction from baseline [and <80 mL/min/1.73 m^2]), where a higher proportion of subjects had events for the "any" time analysis, but the occurrence of such events at the "last" value available was not notably different across groups. In addition, a similar incidence of renal-related adverse events was observed in subjects with NKF Stage 3A and 3B renal disease (ie, eGFR 30 to <45, and 45 to <60 mL/min/1.73 m^2).

Table 28: Overall Summary of Renal-related Adverse Events in Pooled Renal Impairment Dataset

Number (%) of subjects with at least one renal-related adverse event of following types:	Placebo (N=382) n (%)	CANA 100 mg (N=338) n (%)	CANA 300 mg (N=365) n (%)	All CANA (N=703) n (%)	All CANA Minus ----- Placebo ---- Diff(%)	95%CI[a]
Any adverse event[b]	14 (3.7)	30 (8.9)	34 (9.3)	64 (9.1)	5.4	(2.4; 8.5)
Adverse event[b] leading to discontinuation	4 (1.0)	4 (1.2)	6 (1.6)	10 (1.4)	0.4	(-1.2; 1.9)
Adverse event[b] related to study drug[c]	10 (2.6)	10 (3.0)	20 (5.5)	30 (4.3)	1.6	(-0.7; 4.0)
Serious adverse event	5 (1.3)	4 (1.2)	5 (1.4)	9 (1.3)	-0.0	(-1.6; 1.6)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.
[b] Selected renal related adverse events include the prespecified list of acute renal failure preferred terms from a MedDRA query listed in the SAP and the additional preferred terms of Glomerular filtration rate decreased and Blood creatinine increased.
[c] Related to study drug includes following relationships as determined by investigator: possibly related, probably related and very likely related.
Note: Percentages calculated with the number of subjects in each group as denominator and the number of subjects experiencing at least an adverse event regardless of use of rescue medication.
Cross-reference: tae50bb_02_ci_raeren1aci.rtf generated by raeren1aci.sas, 02DEC2012 16:13

6.4.2.6. Adjudicated Renal Events

To determine the potential causality relationship of renal events with study drug, criteria were established to identify potentially clinically important renal failure events (see below), and these adverse events were then submitted for adjudication. The criteria focused on evidence of substantive decline in renal function (see below), either based upon consecutive values or last available value meeting criteria. To assure a comprehensive process, these criteria were applied to laboratory results from the central laboratory or from local laboratory results reported by the investigational sites.

6.4.2.6.1. Adjudication Criteria and Process

Adjudication Criteria

The criteria for identification of renal cases submitted to the CEC for adjudication were as follows:

- **Sustained doubling of serum creatinine from the baseline value (or ≥50% decrease in eGFR from baseline)** that occurred while the subject was on study drug. The definition of "sustained" was a repeat value occurring ≥4 weeks after the initial finding and with the subject having remained on study drug.
- **Doubling in baseline serum creatinine (or ≥50% decrease in baseline eGFR) at last recorded laboratory value.** A "last" value is defined as either last available value in

subjects who completed the study or discontinued early, or as the last value available at the time of study cut-off date in subjects who continued in the study (and may have had follow-up values on drug after study cut-off date).

- **End stage renal disease (ESRD, new or worsening) or renal replacement (dialysis or transplant).** All terms potentially reflecting replacement renal therapy were searched (eg, dialysis, ESRD, transplantation).

Cases meeting above criteria were identified both by review of canagliflozin program laboratory database (results from the program's central laboratory) and by periodic review of reported local laboratory values (eg, during hospitalization) from the sponsor's Global Medical Safety (GMS) database.

Adjudication Process

The renal adjudication process was performed by the Harvard Clinical Research Institute (HCRI), which has extensive experience in conducting renal event adjudication. Harvard Clinical Research Institute adjudicated renal cases independently and was blinded to study group assignment. Causality was provided by HCRI in the following classifications: very likely, probable, possible, doubtful, and not related.

6.4.2.6.2. Adjudicated Events: Results

A total of 43 subjects, balanced across treatment groups, were identified that met any of the renal adjudication criteria for evaluation by the CEC and had adjudication results by 01 July 2012 (Table 29).

Table 29: Summary of Cases Sent for Renal Clinical Events Committee Adjudication

Criteria for Adjudication	All Non-CANA n (%) (N=3640)	CANA 100 mg n (%) (N=3092)	CANA 300 mg n (%) (N=3462)	All CANA n (%) (N=6554)
Any[a]	15 (0.41)	12 (0.39)	16 (0.46)	28 (0.43)
Sustained[b] elevation in serum creatinine	0	0	0	0
Sustained[b] decrease in eGFR	4 (0.11)	0	2 (0.06)	2 (0.03)
Last value elevation in serum creatinine	4 (0.11)	3 (0.10)	5 (0.14)	8 (0.12)
Last value decrease in eGFR	10 (0.27)	6 (0.19)	11 (0.32)	17 (0.26)
ESRD or renal replacement (dialysis or transplant[c])	1 (0.03)	4 (0.13)	1 (0.03)	5 (0.08)

[a] Any refers to any of the following 5 CEC criteria
[b] Sustained increase (decrease) was determined based on the clinical review of the searched results from the database
[c] Based on a clinical and safety database search of selected AE preferred terms; ESRD = end stage renal disease
Note: "Number of Cases" is the number of cases meeting the CEC criteria classification.
Cross-reference: cec0101jul12.rtf generated by cec01.sas, 27AUG2012 09:39

The occurrence of events considered possibly or probably associated with study drug was balanced across treatment groups (0.23% for the combined canagliflozin group and 0.25% for the non-canagliflozin group), with no events considered as "very likely" associated (Table 30).

Table 30: Individual Renal Clinical Event Committee (CEC) Criteria Summary of CEC-determined Causality for Cases Sent for CEC Adjudication (through 01 July 2012)

	All Non-CANA n (%) (N=3640)	CANA 100 mg n (%) (N=3092)	CANA 300 mg n (%) (N=3462)	All CANA n (%) (N=6554)
Number of cases	15	12	16	28
Causality Assigned by CEC:				
Very Likely	0	0	0	0
Probable	1 (0.03)	1 (0.03)	2 (0.06)	3 (0.05)
Possible	8 (0.22)	4 (0.13)	8 (0.23)	12 (0.18)
Doubtful	3 (0.08)	2 (0.06)	4 (0.12)	6 (0.09)
Not Related	3 (0.08)	5 (0.16)	2 (0.06)	7 (0.11)

[a] Any refers to any of the following 5 CEC criteria
Note: "Number of Cases" is the number of cases meeting the CEC criteria classification.
Cross-reference: attachment DCEC04_01JUL12

There were 4 subjects (1 in the canagliflozin 100 mg group, 2 in the canagliflozin 300 mg group, and 1 in the non-canagliflozin group) with renal events that were adjudicated by the CEC as having a "probable" causality relationship with study drug. These events are described below:

- Subject 400812 (canagliflozin 100 mg) was a 39-year-old man with an ongoing medical history of obesity, hyperlipidemia, and hypertension. His concomitant medications included, among others, irbesartan, lisinopril, doxazosin, and torsemide. The subject had a baseline (Day 1) eGFR value of 55 mL/min/1.73 m^2 which was higher compared with the subject's screening (Day -56) and run-in (Day -21) eGFR values (35 and 31 mL/min/1.73 m^2, respectively). The subject discontinued study therapy on Day 221 and his last eGFR value (Day 246) was 28 mL/min/1.73 m^2, meeting the adjudication criterion for a ≥50% reduction in eGFR from the baseline value. The renal event was not reported as an adverse event by the investigator and no other concurrent adverse events were reported at the time of the renal event.
- Subject 804671 (canagliflozin 300 mg) was a morbidly obese 65-year-old man, with an ongoing medical history of hypertension, hyperlipidemia, and obstructive sleep apnea. His concomitant medications included furosemide, felodipine, losartan/hydrochlorothiazide, diltiazem, isosorbide mononitrate, metoprolol, and colchicine (started on Day 156). The subject's screening and baseline eGFR values were 60 and 61 mL/min/1.73 m^2, respectively. On Day 43, the subject had an eGFR of 32 mL/min/1.73 m^2, with repeat values on Day 51 and 127 of 43 and 44 mL/min/1.73 m^2, respectively. On Day 274, an adverse event of renal impairment (verbatim: deteriorating renal function) was reported for the subject, which the investigator considered mild in severity and not related to study drug. This adverse event did not lead to any changes in study drug administration. On Day 372, the subject's last eGFR value (at the time of the database cutoff for adjudication) was 30 mL/min/1.73 m^2, meeting adjudication criteria (≥50% reduction relative to baseline for last eGFR value). Additional values in the sponsor's database obtained after database cutoff (from local laboratory tests) show that the subject's eGFR improved after Day 372, with the value rising to 50 mL/min/1.73 m^2 on Day 508, and then decreased to 34 mL/min/1.73 m^2 on Day 539. Additional information from the investigator showed that the subject's pre-study eGFR

values were 40 mL/min/1.73 m^2 on Day -301 and 57 mL/min/1.73 m^2 on Day -105. The subject remains in the study.

- Subject 801658 (non-canagliflozin) was a 68-year-old man, with medical history including hypertension, hyperlipidemia, acute renal insufficiency, and chronic obstructive pulmonary disease. The subject's concomitant medications included, among others, acetylsalicylic acid, bisoprolol, and vasoretic. No adverse events were reported. The subject had screening (Day -18) and baseline eGFR values of 42 and 78 mL/min/1.73 m^2, respectively. On Day 127, the eGFR was 37 mL/min/1.73 m^2 and on Day 274 the eGFR was 39 mL/min/1.73 m^2, meeting renal adjudication criteria of a sustained reduction in eGFR (a ≥50% reduction in eGFR relative to baseline value for ≥4 weeks). Subsequent to the sustained reduction, while the subject remained in the trial, on Day 365 eGFR was reported as 45 mL/min/1.73 m^2. The subject discontinued the trial on Day 365 (cited as personal reasons); values in the sponsor's database obtained during a follow up visit after database cutoff showed an eGFR and 55 mL/min/1.73 m^2 on Day 547.
- Subject 804565 (canagliflozin 300 mg) was a 76-year-old man with an ongoing medical history of obesity, hypertension, chronic obstructive pulmonary disease, gout and erectile dysfunction. The subject also had ongoing chronic stage II kidney disease. His concomitant medications included, among others, atenolol, benazepril, acetylsalicylic acid and indomethacin. The subject had a baseline (Day 1) eGFR value of 66 mL/min/1.73 m^2 which was higher compared with the subject's screening (Day -21) eGFR value of 58 mL/min/1.73 m^2. The subject had eGFR values of 50 mL/min/1.73 m^2, 43 mL/min/1.73 m^2, 41 mL/min/1.73 m^2 and 44 mL/min/1.73 m^2 on Days 43, 127, 331 and 365, respectively. On Day 541 the subject's eGFR value was 31 mL/min/1.73 m^2, meeting the adjudication criterion for a ≥ 50% reduction in eGFR from the baseline value. On Day 541 an adverse event of diabetic nephropathy was reported, which was considered by the investigator to be mild in severity, not serious and unrelated to the study drug. The dose of study drug was not changed due to the adverse event, and the subject remains in the study.

Among the subjects submitted for renal adjudication were 6 subjects with ESRD or replacement (dialysis or transplant). All 6 subjects met the adjudication criteria based upon initiation of hemodialysis. The distribution of the subjects was as follows: 1 subject in the non-canagliflozin group, 4 subjects in the canagliflozin 100 mg group, and 1 subject in the canagliflozin 300 mg group. Of the 6 cases submitted for adjudication based upon initiation of hemodialysis, 4 cases were adjudicated as "not related" to study drug and 1 case was adjudicated as "doubtful". One case (on canagliflozin 300 mg) was adjudicated with a causality of "possibly" related to study drug and is described below.

- Subject 804929 (canagliflozin 300 mg), a 62-year-old woman with medical history of hypertension, chronic pyelonephritis, coronary artery disease, and stable angina, with a baseline moderate chronic renal failure. The subject's concomitant medications at baseline were lisinopril, bisoprolol, and acetylsalicylic acid. Screening (Day -21) eGFR was 41 mL/min/1.73 m^2 and at baseline, eGFR was 46 mL/min/1.73 m^2. The subject had a serious adverse event of chronic renal failure on Day 92 (concurrent renal function tests not reported), that required hospitalization on Day 108 and initiation of hemodialysis on Day 116. No information on renal function at the time of hospitalization and potential precipitating factors could be obtained from the subject and investigational site despite several attempts. The investigator considered the serious adverse event not related to study

drug, and the subject discontinued on Day 106. A follow-up renal test obtained on Day 172 showed a further worsening in renal function (eGFR 7 mL/min/1.73 m^2). The subject died on Day 290 due to hepatic cirrhosis, reported on Day 288 as a serious adverse event, not related to study drug.

6.4.2.7. Summary and Conclusions for Changes in Measures of Renal Function

Treatment with canagliflozin leads to small reductions from baseline in eGFR that were generally stable or improved with continued treatment. The percent reductions were larger in the subjects with reduced renal function (eGFR ≥30 to <60 mL/min/1.73 m^2), but with a similar pattern of an early reduction followed by eGFR trending towards baseline. Analyses of eGFR post-discontinuation showed reversibility of the modest reductions seen on canagliflozin.

The proportion of subjects with larger reductions in eGFR (meeting pre-specified change criteria) was higher on canagliflozin when examining any measurement during the double-blind period (with those meeting the change criterion most commonly at the initial measurement at Week 6); however, the proportion of subjects with the last on-study drug value meeting the criteria was low, similar in the canagliflozin 100 mg group relative to the non-canagliflozin group, and only slightly higher in the canagliflozin 300 mg group. This is similar to the occurrence of adverse events related to reduced intravascular volume—occurring early after initiation of canagliflozin—and is consistent with the concept that reductions in eGFR are related to reductions in intravascular volume; resolution of these small reductions in eGFR (during continued treatment or posttreatment) are also consistent with a hemodynamic mechanism, and not suggestive of renal injury. Follow-up of subjects with larger decreases in eGFR (meeting the pre-specified criteria) and of subjects with renal-related adverse events, showed that a high proportion resolved (either continuing on drug or after discontinuation), consistent with a volume-related (ie, pre-renal) pattern. Finally, the biomarker of renal injury, the urinary ACR, did not increase in subjects treated with canagliflozin who were normoalbuminuric at baseline, and decreased in subjects with baseline albuminuria (either micro- or macroalbuminuria).

Subjects with more substantial decreases in renal function (ie, ≥50% last or sustained decrease in eGFR) were infrequent—and underwent adjudication by an external EAC. The incidence of events meeting these criteria was balanced across treatment groups, as was the infrequent occurrence of events considered by the EAC as probably or possibly-related to study drug. Consistent with this, the incidence of renal-related serious adverse events was similar across treatment groups in both the Broad Dataset and in the Pooled Renal Impairment Dataset.

In summary, analysis of mean changes in eGFR, incidence of larger decreases in eGFR, renal-related adverse events, and post-discontinuation follow-up assessments suggest that treatment with canagliflozin can lead to a small decrease in glomerular filtration rate related to a hemodynamic (pre-renal) mechanism. These small changes are reversible while continuing on canagliflozin or after treatment discontinuation. No evidence for renal injury was noted with canagliflozin treatment.

6.5. Bone Safety Assessments

6.5.1. Introduction

As discussed in Section 2, in rat toxicology studies, hyperostosis (increased trabecular bone content) was observed. This was associated with carbohydrate malabsorption, leading to calcium hyperabsorption, marked hypercalciuria (increases of > 10-fold), and decreases in PTH and 1,25 dihydroxyvitamin D and in markers of bone turnover. These effects are related to canagliflozin inhibition of SGLT1 in rats, which induces carbohydrate malabsorption. As discussed in Section 2, interventions (eg, a glucose/galactose free diet) in the rat that prevented carbohydrate malabsorption inhibited hypercalciuria, decreases in PTH, 1,25 dihydroxyvitamin D and markers of bone turnover, and hyperostosis. In clinical studies, canagliflozin transiently reduces intestinal glucose absorption, but does not induce malabsorption (based upon both dual tracer studies [DIA1022] examining overall glucose absorption and a hydrogen breath test [DIA1007]). As discussed in the next section, in clinical studies, no discernible effects on serum calcium or urinary calcium excretion are seen, and no sustained effects on PTH or 1,25 dihydroxyvitamin D are observed. Nonetheless, based upon the observation in rat toxicology studies of hyperostosis in the rats with canagliflozin treatment, additional clinical evaluations were performed in Phase 1 through 3 studies to support the assessment of bone safety.

6.5.2. Laboratory Evaluations of Calcium Axis

Serum Calcium, Phosphate, Magnesium, and PTH

No discernible mean changes from baseline in serum calcium have been observed with canagliflozin treatment, including in subjects in the dedicated study in subjects with lower eGFR (DIA3004, eGFR 30 to ≤ 50 mL/min/1.73 m2). Similarly, no meaningful changes in urinary calcium excretion are observed. In Phase 2 studies, a small transient increase in PTH was seen (at Week 3), that returned to baseline values by Week 12. In the DIA3010 study (older subjects with T2DM), PTH was measured at Weeks 26 and 52, with minimal changes seen at either time point with canagliflozin relative to placebo (LS mean changes from baseline of 7.4% and 2.5% in the canagliflozin 100 mg and 300 mg groups, respectively, and 0.5% in the placebo group at Week 26, and LS mean changes from baseline of 12.2% and 7.5% in the canagliflozin 100 mg and 300 mg groups, respectively, and 6.1% in the placebo group at Week 52). In the DIA3004 study, relative to placebo, small reductions in PTH were seen in the canagliflozin 100 mg and 300 mg groups (-10.3% and -16.1%, respectively) (with the 95% CIs around the between-group differences with placebo including "0"). Despite these placebo-subtracted LS mean decreases in PTH in the canagliflozin groups, the absolute mean PTH values started and ended slightly higher in the canagliflozin groups relative to the placebo group. No meaningful changes in 25-hydroxyvitamin D or 1-25 dihydroxvitamin D were seen in the Phase 2 studies (not measured in Phase 3 studies).

Small to moderate, dose-dependent increases at Week 26 in serum phosphate were seen with canagliflozin in the Placebo-controlled Studies Dataset: mean percent increases of 3.6% and 5.1% in the 100 mg and 300 mg groups, respectively. Small to moderate mean percent increases from baseline in serum magnesium were also observed at Week 26 in the canagliflozin 100 mg

and 300 mg groups (8.1% and 9.3%, respectively) compared with the placebo group (-0.6%) in the Placebo-controlled Studies Dataset. The increases in serum phosphate and magnesium were first observed at Week 6 and remained stable throughout the 26 weeks period. Few adverse events reflecting either an increase in serum phosphate or serum magnesium were reported with canagliflozin; none were serious or led to discontinuation. In subjects with renal impairment (eGFR ≥30 to <50 mL/min/1.73 m^2, study DIA3004), mean percent serum phosphate increases of 4.6% and 9.4% for the canagliflozin 100 mg and 300 mg groups and 1.1% for the placebo group were observed. Slightly smaller median percent changes (4.4% and 7.0% for canagliflozin 100 mg and 300 mg groups, respectively, with no change in the placebo group) were seen. Mean changes in serum magnesium in this study were similar to those observed in the Placebo-controlled Studies Dataset.

In summary, no notable changes in serum calcium, urinary calcium, 1,25 dihydroxyvitamin D, or PTH are seen with canagliflozin treatment. Increases in serum phosphate and magnesium are observed with canagliflozin and have been described with other SGLT2 inhibitors (Dapagliflozin FDA Briefing Book) that are small and not likely to be clinically relevant.

Bone Turnover Markers

Markers of bone turnover and bone formation were examined in the 12 week Phase 2b study in subjects with T2DM (DIA2001) and in the study in older subjects with T2DM examining bone safety (DIA3010). In the Phase 2 study, serum beta-CTx levels increased approximately 20 to 25% after 12 weeks; in Study DIA3010, similar increases in serum beta-CTx were seen after 26 weeks, with slightly smaller increases after 52 weeks (Table 31). After 12 weeks in the Phase 2 study, there was no discernible change in serum osteocalcin, a marker of bone formation; however, in Study DIA3010 osteocalcin modestly increased after 26 weeks, and further increased after 52 weeks of treatment with canagliflozin (Table 32). The gradual rise in osteocalcin over the 52 week treatment period is consistent with expectations with regard to timing of changes in bone formation after an increase in bone resorption, as evidenced by the serum beta-CTx increase. In contrast, small decreases relative to placebo in P1NP, another bone formation marker, were seen after 26 weeks; however, the changes were variable and the 95% CI for the mean placebo-subtracted difference for P1NP included "0" for both doses of canagliflozin.

Weight loss has been demonstrated to lead to increases in bone turnover (Hinton 2012, Hyldstrup 1993, Shapses 2001). Analyses were conducted to determine if the increases in the bone turnover markers were related to the changes in weight with canagliflozin treatment: statistically significant correlations were seen in the relationship between changes from baseline in serum beta-CTx and body weight at both Weeks 26 and 52 for both doses of canagliflozin. Similar relationships were seen with serum osteocalcin and body weight at Week 52 (only minimal changes in serum osteocalcin were observed at Week 26), that was significant for the canagliflozin 300 mg group and trended toward significance for the canagliflozin 100 mg group. These results are consistent with the reports in the literature on the relationship weight loss and increases in bone turnover and formation, and the increases observed are consistent with the extent of increases observed with weight loss.

Table 31: Serum Beta-CTx: Percent Change from Baseline to Week 52 (Study DIA3010)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Serum collagen type 1 beta carboxy telopeptide (µg/L)			
Value at Baseline			
N	165	202	185
Mean (SD)	0.36 (0.19)	0.35 (0.18)	0.33 (0.16)
Value at Week 52			
N	165	202	185
Mean (SD)	0.36 (0.19)	0.39 (0.20)	0.41 (0.21)
% Change from Baseline			
N	165	202	185
Mean (SD)	5.1 (31.03)	15.7 (38.91)	28.2 (49.63)
LS Mean (SE)	5.6 (3.93)	15.9 (3.98)	27.6 (4.05)
Diff. of LS Means (SE)(minus Placebo)		10.3 (4.19)	22.0 (4.27)
95% CI[a]		(2.1;18.6)	(13.6;30.4)

[a] Pairwise comparison: CIs are based on the ANCOVA model with treatment, sex, T-score of lumbar spine (<-1.5 or ≥- 1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline serum beta-CTx measurement.

Note: The table includes only the subjects who had both baseline and postbaseline serum beta-CTx Measurement.
Cross-reference: tlb144_52wrbslsmean.rtf generated by rbslsmean.sas, 16NOV2012 13:57

Table 32: Serum Osteocalcin: Percent Change from Baseline to Week 52 (Study DIA3010)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Serum osteocalcin (µg/L)			
Value at Baseline			
N	162	200	187
Mean (SD)	14.10 (6.14)	13.83 (5.36)	13.92 (5.11)
Value at Week 52			
N	162	200	187
Mean (SD)	14.46 (6.68)	15.35 (6.05)	15.73 (5.90)
% Change from Baseline			
N	162	200	187
Mean (SD)	5.1 (26.07)	14.8 (33.23)	15.2 (25.40)
LS Mean (SE)	8.7 (2.75)	18.1 (2.78)	18.8 (2.82)
Diff. of LS Means (SE)(minus Placebo)		9.4 (2.94)	10.1 (2.98)
95% CI[a]		(3.6;15.2)	(4.3;16.0)

[a] Pairwise comparison: CIs are based on the ANCOVA model with treatment, sex, T-score of lumbar spine (<-1.5 or ≥- 1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline osteocalcin measurement.

Note: The table includes only the subjects who had both baseline and postbaseline osteocalcin measurement.
Cross-reference: tlb114_52wrbslsmean.rtf generated by rbslsmean.sas, 16NOV2012 13:57

6.5.3. Assessment of Bone Density: Dual Energy X-Ray Absorptiometry (DXA)

Bone density was assessed in study DIA3010 (study in subjects ≥55 to ≤80 years old) using a central, blinded reading process. The low variability in the DXA results in this study allowed a precise and robust assessment of bone density. Density was examined at 4 sites with the primary site of interest the lumbar spine. Results from the 52-week assessments are completed (subsequent assessment at Week 104 is pending) and are described below.

As shown in Table 33, for the lumbar spine (a site of predominantly trabecular bone), decreases in bone density, relative to placebo, with canagliflozin 100 mg and 300 mg were observed at Week 52 (with the 95% CI around the between group difference relative to placebo not including "0" for canagliflozin 300 mg); the absolute changes from baseline were small for both canagliflozin doses, with larger reductions in women relative to men.

Other sites examined included the distal third of the forearm (a site of predominantly cortical bone), femoral neck (a site of mixed cortical and trabecular bone), and total hip (a site of mixed cortical and trabecular bone). At Week 52, there was a small dose-dependent decrease in total hip bone density, relative to placebo, with canagliflozin 100 mg and 300 mg at Week 52 (with the 95% CI around the between group difference relative to placebo not including "0" for canagliflozin 300 mg) with larger reductions seen in female relative to male subjects. In contrast to the total hip, at the femoral neck, a slight increase in bone density with canagliflozin relative to placebo was noted and similarly, slight increases with canagliflozin relative to placebo in the

distal forearm BMD (a cortical site) by DXA were observed relative to placebo. For both of these sites, the 95% CI around the between-group differences relative to placebo included "0" (Table 33).

Table 33: Bone Density Measurements: Percent Change From Baseline to Week 52 (Study DIA3010)

	Placebo (N=237)	CANA 100 mg (N=241)	CANA 300 mg (N=236)
Lumbar spine corrected BMD measurement			
% Change from Baseline			
N	170	201	190
Mean (SD)	0.4 (2.91)	-0.1 (3.52)	-0.3 (3.33)
LS Mean (SE)	0.6 (0.33)	0.2 (0.34)	-0.1 (0.34)
Diff. (%) of LS Means (SE)(minus Placebo)		-0.4 (0.34)	-0.7 (0.34)
95% CI[a]		(-1.0;0.3)	(-1.4;-0.1)
Distal forearm corrected BMD measurement[b]			
% Change from Baseline			
N	172	205	185
Mean (SD)	-0.6 (3.14)	-0.2 (3.12)	-0.6 (3.58)
LS Mean (SE)	-0.6 (0.32)	-0.1 (0.33)	-0.5 (0.33)
Diff. (%) of LS Means (SE)(minus Placebo)		0.5 (0.34)	0.1 (0.34)
95% CI[a]		(-0.1;1.2)	(-0.6;0.7)
Femoral neck corrected BMD measurement			
% Change from Baseline			
N	172	206	189
Mean (SD)	-1.3 (3.06)	-1.2 (4.01)	-0.7 (3.63)
LS Mean (SE)	-1.5 (0.36)	-1.4 (0.36)	-0.9 (0.36)
Diff. (%) of LS Means (SE)(minus Placebo)		0.1 (0.38)	0.6 (0.38)
95% CI[a]		(-0.6;0.8)	(-0.1;1.4)
Total hip corrected BMD measurement			
% Change from Baseline			
N	172	206	189
Mean (SD)	-0.3 (1.98)	-0.7 (2.97)	-1.0 (2.47)
LS Mean (SE)	-0.7 (0.25)	-1.1 (0.25)	-1.5 (0.26)
Diff. (%) of LS Means (SE)(minus Placebo)		-0.4 (0.26)	-0.7 (0.27)
95% CI[a]		(-1.0;0.1)	(-1.3;-0.2)

[a] Pairwise comparison: CIs were based on an ANCOVA model with treatment, sex, T-score of lumbar spine (<-1.5 or ≥-1.5) based on central reading, and on or not on a PPARγ agent based on concomitant medication history, and baseline bone density measurement.

[b] Distal forearm: region of interest, 1/3 radius (33% radius).

Note: The table includes only the subjects who had both baseline and postbaseline measurements.

Cross-reference: attachments DBS04_MA_DX52_52W, DBS04_MB_DX52_52W, DBS04_MC_DX52_52W, and DBS04_MD_DX52_52W

As previously noted (see Section 6.5.2), increases in bone turnover are observed with weight loss; similarly, an extensive literature has shown that decreases in bone density are consistently observed with weight loss, especially in older individuals (Schwartz 2012, Bleicher 2011), the target population in this study. The impact of weight loss associated decreases in BMD on fracture risk in patients with T2DM is unknown. In patients undergoing bariatric surgery, which is associated with a much greater extent of weight loss and therefore BMD reductions, fracture

risk is not increased during 2.2 years after the surgery. However, trends for excess fracture risk 3 to 5 years after bariatric surgery and in patients who had greater postsurgical reductions in BMI were observed (Lalmohamed 2012). Given region to region variability in BMD, the relationship of changes in body weight to changes in total body BMD was examined (total BMD was measured in the DIA3009 study) at Week 52; this analysis showed that changes in total body BMD were significantly correlated (p=0.002) with changes in body weight. In a model-based analysis, when a term for absolute change in body fat (by DXA) was included in the model, the decreases in total BMD with canagliflozin treatment were no longer seen, supporting the conclusion that these changes are likely related to weight loss.

These observations are supportive of the assessment that the decrease in body weight with canagliflozin likely underlies the small reductions in BMD seen at 2 of the 4 sites evaluated. The observation that the rise in serum CTx and the increase in serum osteocalcin were generally comparable at Week 52 would indicate balanced turnover and formation occurring at this time point; in association with the weight changes which are stable at Week 52, this would suggest that no further changes in BMD are likely to be observed. The results from Week 104 will be necessary to confirm this assessment.

6.5.4. Fracture Adverse Events

In the canagliflozin Phase 3 program, bone safety assessment included adjudication of all clinical fractures in the Phase 3 program to determine the type of fracture (eg, low trauma, high trauma, pathologic), with the primary analysis based on low trauma and all adjudicated fractures.

6.5.4.1. Data Collection and Analysis

Events for the analysis were reported on the general adverse event eCRF page by the investigator and then on the supplemental eCRF for fractures (including collection of a narrative of the event, describing the circumstances). All fracture adverse events were then adjudicated by an independent, blinded fracture adjudication committee to confirm that events were fractures, for the type of fracture (low trauma, high trauma, pathologic, stress and other), and the location of the fracture. As noted in the introduction, the focus was on low trauma and all adjudicated fractures (see Attachment 20 for specific definitions used).

To provide the longest exposure, pooled summaries and analyses of fracture adverse events were based on the Broad Dataset (results through 01 July 2012). The primary analysis included all postrandomization events including events >30 days after the last dose of study drug. This analysis was selected since any changes in bone susceptibility related to canagliflozin would be expected to persist given the gradual onset and resolution of the impact of drugs on bone health.

6.5.4.2. Results

A modestly higher incidence of adverse events of fractures in the Broad Dataset (results through 01 July 2012; primary analysis, all postrandomization events) was observed in the combined canagliflozin group relative to the non-canagliflozin group (Table 34). Given differences in duration of exposure across groups (See Section 6.1.2), the incidence rates per 1000 subject-years of exposure were assessed. A modestly higher incidence rate per

1000 subject-years was observed with canagliflozin (18.11 and 14.16 for the combined canagliflozin and non-canagliflozin groups, respectively) with the 95% CI around the between-group difference including "0". For adjudicated low trauma fractures, a modestly higher incidence was observed in the combined canagliflozin group relative to the non-canagliflozin group (Table 34). The incidence rate per 1,000 subject-years exposure for low trauma fractures were 12.51 and 12.04 years in canagliflozin 100 mg and 300 mg groups, compared to 9.44 years in non-canagliflozin group, with the 95% CI around the between-group difference including "0". Overall fracture rates were higher in women than in men, as expected.

Table 34: Post Randomization Fracture Adverse Events by Fracture Type in Broad Dataset (through 01 July 2012)

Fracture Type	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)	CANA 100 mg Minus -All Non-CANA - Diff	95%CI[b]	CANA 300 mg Minus -All Non-CANA - Diff	95%CI[b]	All CANA Minus -All Non- CANA - Diff	95%CI[b]
Total no. subjects with adverse events[c]	57 (1.7)	76 (2.5)	70 (2.3)	146 (2.4)	0.7	(-0.0; 1.4)	0.5	(-0.2; 1.2)	0.6	(0.0; 1.2)
Incidence rate per 1000 subject-years exposure (SE)	14.16 (1.89)	18.65 (2.15)	17.56 (2.11)	18.11 (1.50)	4.5	(-1.14; 10.10)	3.4	(-2.17; 8.95)	3.9	(-0.79; 8.68)
Total no. subjects with Adjudicated Fracture Type[c]	53 (1.6)	68 (2.2)	61 (2.0)	129 (2.1)	0.6	(-0.1; 1.3)	0.4	(-0.3; 1.0)	0.5	(-0.1; 1.0)
High trauma	11 (0.3)	15 (0.5)	12 (0.4)	27 (0.4)	0.1	(-0.2; 0.5)	0.1	(-0.3; 0.4)	0.1	(-0.2; 0.4)
Impact unknown	0	1 (<0.1)	0	1 (<0.1)	0.0	(-0.1; 0.1)	0.0	(-0.0; 0.0)	0.0	(-0.0; 0.1)
Low trauma	38 (1.2)	51 (1.6)	48 (1.6)	99 (1.6)	0.5	(-0.1; 1.1)	0.4	(-0.2; 1.0)	0.4	(-0.1; 0.9)
Pathological	0	0	1 (<0.1)	1 (<0.1)	0.0	(-0.0; 0.0)	0.0	(-0.1; 0.1)	0.0	(-0.0; 0.1)
Possible unknown trauma	0	0	1 (<0.1)	1 (<0.1)	0.0	(-0.0; 0.0)	0.0	(-0.1; 0.1)	0.0	(-0.0; 0.1)
Stress	3 (<0.1)	1 (<0.1)	0	1 (<0.1)	-0.1	(-0.2; 0.1)	-0.1	(-0.2; 0.0)	-0.1	(-0.2; 0.1)
Unknown	1 (<0.1)	0	1 (<0.1)	1 (<0.1)	-0.0	(-0.1; 0.1)	0.0	(-0.1; 0.1)	-0.0	(-0.1; 0.1)

[a] Denotes the difference in the incidence rate or the difference in proportion of subjects with the adverse event

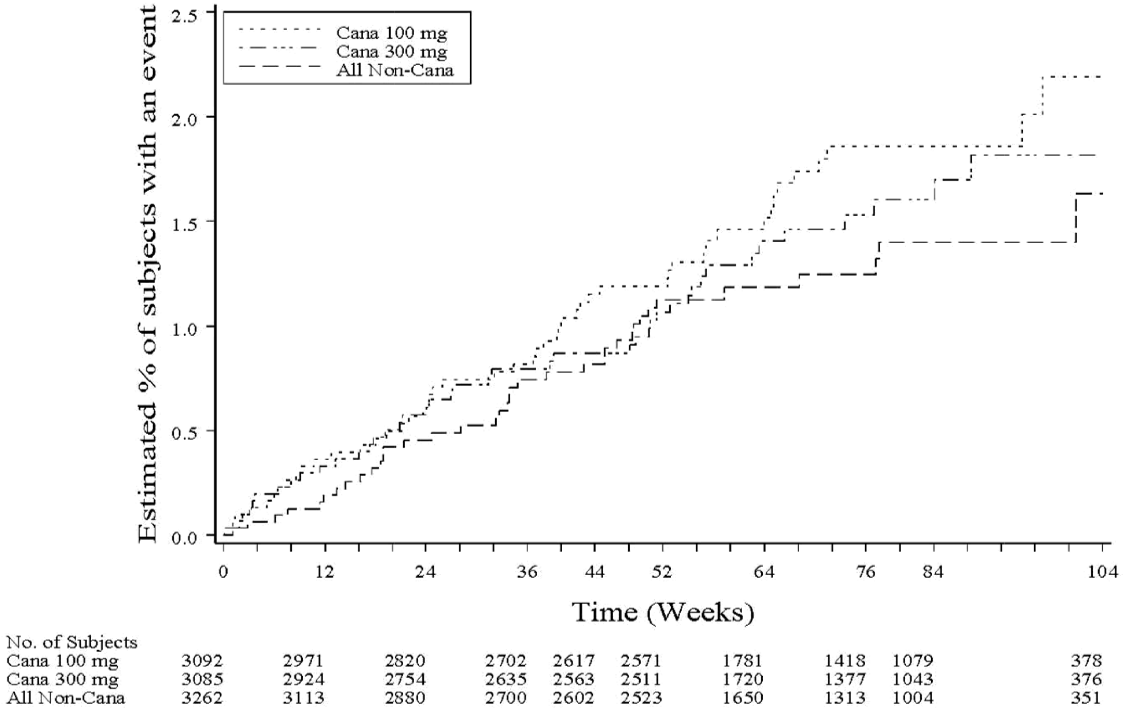
[b] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

[c] Fracture adverse events based upon a prespecified subset of preferred terms from a MedDRA query listed in the SAP.

Cross-reference: tae40frtypesensn0401jul12raefract6sensn.rtf generated by raefract6sensn.sas, 07SEP2012 12:05

A time to event analysis of low trauma fractures in the Broad Dataset showed more events in the canagliflozin groups compared with the non-canagliflozin groups within the first 12 weeks after randomization (Figure 33), without consistent further separation in the curves. This early separation was not as notable in the time to event analysis for overall adjudicated fractures.

Figure 33: Kaplan-Meier Plot of Time to First Low Trauma Fracture Adverse Event in Broad Dataset (through 01 July 2012)



No. of Subjects										
Cana 100 mg	3092	2971	2820	2702	2617	2571	1781	1418	1079	378
Cana 300 mg	3085	2924	2754	2635	2563	2511	1720	1377	1043	376
All Non-Cana	3262	3113	2880	2700	2602	2523	1650	1313	1004	351

With regard to regional distribution of fracture events, lower limb fractures were evenly distributed across treatment groups while a greater numbers of subjects experienced low trauma upper limb fractures in the canagliflozin groups: 22 (0.7%) and 22 (0.7%) subjects in the canagliflozin 100 mg and 300 mg groups, respectively, and 11 (0.3%) subjects in the non-canagliflozin group. The trend toward a higher incidence of upper limb fractures in the canagliflozin group relative to the non-canagliflozin group was more evident in women than in men. The distribution of the reported upper limb fractures included a range of sites (Table 35).

Table 35: Distribution of Low Trauma Upper Limb Fracture in Broad Dataset (through 01 July 2012)

Dictionary-Derived Term	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)
Hand Fracture	6 (0.2)	8 (0.3)	10 (0.3)	18 (0.3)
Humerus Fracture	2 (0.1)	4 (0.1)	7 (0.2)	11 (0.2)
Radius Fracture	4 (0.1)	4 (0.1)	2 (0.1)	6 (0.1)
Ulna Fracture	0	2 (0.1)	0	2 (<0.1)
Upper Limb Fracture	1 (<0.1)	2 (0.1)	4 (0.1)	6 (0.1)
Wrist Fracture	4 (0.1)	7 (0.2)	3 (0.1)	10 (0.2)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events regardless of use of rescue medication.
Cross-reference: DAE37FRSENS_04_01JUL12

Any negative impact an agent may have on bone health would be expected to take months to accrue to increase susceptibility to fractures; based upon this, the small increase seen within weeks of initiation of treatment would not be suggestive of impaired bone health leading to increased fracture susceptibility. Since fractures may occur related to either a decrease in bone health or to an increase in trauma due to falls, a careful review of narratives describing the fracture event (collected for all fracture adverse events) and any potentially related adverse events, including falls, was conducted. This assessment did not show an association of the upper limb fractures with adverse events of reduced intravascular volume or of hypoglycemia events; there was no discernible difference in the incidence of adverse events of falls in the canagliflozin relative to the non-canagliflozin groups; finally, review of laboratory parameters and BP over the course of 18 weeks in subjects experiencing low trauma fractures on canagliflozin, compared with the overall population on canagliflozin, showed no notable differences in changes from baseline in hemoglobin, BUN, creatinine, and blood pressure, suggesting that the subjects with low trauma fractures were not at higher risk for volume-related changes relative to the overall population studied. These assessments did not confirm that the early small increase in upper limb fracture adverse events seen in the canagliflozin groups was related to the occurrence of reduced intravascular volume-related adverse events or to hypoglycemia. However, it is not possible to exclude the possibility that the effects of reduced intravascular volume contributed to the early imbalance in these fracture events. As discussed in Section 6.3.5, the proposed labeling for canagliflozin will clearly indicate that this agent has a diuretic action (as an osmotic diuretics) so that physicians can appropriately manage patients with initiation of this agent.

6.5.5. Summary and Conclusions

Results from 52-week DXA assessments showed small reductions at 2 of 4 sites examined (total hip and lumbar spine) that are likely related to the weight loss provided by canagliflozin treatment, given the relationships demonstrated between changes in bone turnover and formation markers and changes in weight, and changes in total body BMD and weight with canagliflozin treatment. Considering the small extent of the changes and the inconsistent BMD results at different sites examined, it would seem unlikely that any meaningful increase in fracture risk would result.

A small, non-dose-related numerical imbalance in overall and low trauma (adjudicated) fractures were observed that were not statistically significant. The imbalance in low trauma fractures was particularly notable early postrandomization and largely related to an imbalance in upper limb fractures. Dual energy X-ray absorptiometry assessed distal forearm bone density was not meaningfully reduced with canagliflozin treatment. Further assessment of this initial difference in low trauma fracture occurrence could not confirm an association of the early fracture events and adverse events of reduced intravascular volume. However, proposed labeling will clearly indicate that canagliflozin has a diuretic action (as an osmotic diuretic), and reduced intravascular volume-related adverse events (eg, postural dizziness) will be described in the label as an ADR for canagliflozin.

6.6. Hypoglycemia

6.6.1. Introduction and Methods

Canagliflozin lowers the mean RT_G to approximately 70 to 90 mg/dL in subjects with T2DM. Since this is above the usual threshold for hypoglycemia, and no further UGE would occur when plasma glucose concentrations fall below the RT_G, the risk of hypoglycemia with canagliflozin treatment was expected to be low when this agent is not used in combination with agents associated with hypoglycemia. In Phase 1 and 2 studies of canagliflozin, both in non-diabetic subjects and in subjects with T2DM, the incidence of hypoglycemia did not appear to be increased with canagliflozin treatment.

In the Phase 3 program for canagliflozin, a detailed evaluation of hypoglycemia was performed across studies. A separate eCRF was implemented to collect information on potential events of hypoglycemia. The primary analysis for hypoglycemia was based on documented episodes of hypoglycemia (defined as an episode with a biochemically documented event [fingerstick glucose of ≤70 mg/dL regardless of the presence of symptoms] *or* a severe hypoglycemic episode [ie, requiring the assistance of another person, or resulting in the loss of consciousness or a seizure], not requiring biochemical documentation).

In studies in which subjects were enrolled on any approved background AHA, analyses for hypoglycemia separately evaluated the incidence and pattern of hypoglycemia events in subjects on agents associated with hypoglycemia (eg, insulin or SU agents) and in subjects not on agents associated with hypoglycemia (eg, metformin, DPP-4 inhibitors, thiazolidinediones).

6.6.2. Incidence and Characteristics of Hypoglycemia in Phase 3 Studies

To assess the incidence of hypoglycemia events in subjects not on the background of an AHA associated with hypoglycemia, an analysis was conducted in subjects from studies in the Placebo-controlled Studies Dataset that did not include such agents (ie, the monotherapy study [DIA3005], the add-on to metformin study [DIA3006], and the add-on to metformin/pioglitazone study [DIA3012], omitting the add-on to metformin/SU study [DIA3002]). In this pooled population, the incidence of hypoglycemic episodes was overall low, slightly higher in the canagliflozin 100 mg (3.8%) and 300 mg groups (4.3%) relative to the placebo group (2.2%) (Table 36). The event rates per subject-year exposure for the canagliflozin 100 mg and 300 mg

groups were greater (0.22 and 0.18, respectively) relative to placebo group (0.10), and with no apparent dose-relationship. The incidence of severe hypoglycemia was low, with 1 subject in each canagliflozin group reported to have had a severe hypoglycemic episode.

Table 36: Documented Hypoglycemia (Placebo-controlled Studies Dataset Excluding DIA3002) Prior to the Use of Rescue Medication

	Placebo (N=490) n (%)	CANA 100 mg (N=676) n (%)	CANA 300 mg (N=678) n (%)	All CANA (N=1354) n (%)	All CANA Minus ---- Placebo ---- 95%CI[a]
Incidence rate per subject-year exposure	0.05	0.08	0.09	0.09	(0.00; 0.08)
Subjects with any documented hypoglycemia	11 (2.2)	26 (3.8)	29 (4.3)	55 (4.1)	(0.00, 3.64)
Biochemically documented hypoglycemia	11 (2.2)	26 (3.8)	28 (4.1)	54 (4.0)	
Severe hypoglycemia	0	1 (0.1)	1 (0.1)	2 (0.1)	
Total number of episodes	20	69	57	126	
Subjects with numbers of documented hypoglycemia	11 (2.2)	26 (3.8)	29 (4.3)	55 (4.1)	(0.00, 3.64)
1 episode	8 (1.6)	15 (2.2)	15 (2.2)	30 (2.2)	
2 episodes	2 (0.4)	3 (0.4)	7 (1.0)	10 (0.7)	
≥3 episodes	1 (0.2)	8 (1.2)	7 (1.0)	15 (1.1)	
Event rate per subject-year exposure	0.10	0.22	0.18	0.20	
Subjects with any biochemically documented hypoglycemia	11 (2.2)	26 (3.8)	28 (4.1)	54 (4.0)	(-0.07,3.56)
≤70 mg/dL (3.9 mmol/L)	11 (2.2)	26 (3.8)	28 (4.1)	54 (4.0)	
<63 mg/dL (3.5 mmol/L)	7 (1.4)	14 (2.1)	16 (2.4)	30 (2.2)	
<56 mg/dL (3.1 mmol/L)	2 (0.4)	5 (0.7)	4 (0.6)	9 (0.7)	
<36 mg/dL (2.0 mmol/L)	2 (0.4)	1 (0.1)	0	1 (0.1)	

[a] CI for pairwise comparison using normal approximation for the difference in rates.

Note: Count (%) is based on number of subjects, not number of events, prior to use of rescue medication.

Note: Documented hypoglycemia includes biochemically documented hypoglycemia (episodes with concurrent glucose measurement ≤70 mg/dL [3.9 mmol/L] regardless of the presence of symptoms) and/or meeting criteria for severe hypoglycemia (not requiring biochemical documentation).

Note: Exposure adjusted incidence rate is calculated as the total number of subjects with at least one event divided by the total drug exposure in subject-years. Exposure adjusted event rate is calculated as the total number of events divided by the total drug exposure in subject-years.

Note: Glucose data could be reported in either mg/dL or mmol/L units. No conversion between the two units was made. The comparison between the reported glucose values and the cutoffs was based on the units in which the glucose values were reported. Results of LOW is included in all the four glucose categories (i.e., ≤70, <63, <56, and/or <36 mg/dL).

Cross-reference: attachment DAE11HYP_01 and attachment DAE12BIOHYP_01

In the active-comparator (glimepiride) controlled add-on to metformin study (DIA3009), the incidence of documented hypoglycemic episodes was significantly lower ($p<0.001$) in the canagliflozin 100 mg (5.6%) and canagliflozin 300 mg groups (4.9%) relative to the active (glimepiride) control group (34.2%) (Table 37). The event rates per subject-year exposure for the canagliflozin 100 mg and 300 mg groups were lower (0.16 and 0.08, respectively) relative to the active (glimepiride) control group (1.72). The number of subjects reported to have severe hypoglycemic episodes was lower in the combined canagliflozin group (5 subjects), relative to the active (glimepiride) control group (15 subjects).

To examine the incidence of hypoglycemia episodes in subjects on the background of agents associated with hypoglycemia, studies with add-on to either an SU or insulin were examined

(Table 37). Across each study, there was a moderate, dose-related increase in the incidence of hypoglycemia with canagliflozin treatment, with a low incidence of severe hypoglycemia events, not increased with canagliflozin relative to comparator or placebo. In the active-controlled study DIA3015 (active-comparator [sitagliptin] controlled add-on to metformin/SU study), the incidence of documented hypoglycemia and severe hypoglycemia was similar in the canagliflozin and sitagliptin treatment groups.

Table 37: Documented Hypoglycemia (Biochemically Documented and/or Severe) - (Studies DIA3002, DIA3008, and DIA3015) Prior to the Use of Rescue Medication

						All CANA Minus ---- Placebo[a] ----	
	Placebo	Active Comparator	CANA 100 mg	CANA 300 mg	All CANA	Diff(%)	95%CI[b]
DIA3002	(N=156)	NA	(N=157)	(N=156)	(N=313)		
Subjects with any documented hypoglycemia	24 (15.4)	NA	43 (27.4)	47 (30.1)	90 (28.8)	13.4	(5.3; 21.4)
Biochemically documented hypoglycemia[c]	24 (15.4)	NA	42 (26.8)	47 (30.1)	89 (28.4)	13.0	(5.0; 21.1)
Severe hypoglycemia	1 (0.6)	NA	1 (0.6)	0	1 (0.3)	-0.3	(-2.2; 1.6)
Total number of episodes	69	NA	184	239	423		
Event rate per subject-year exposure	1.04	NA	2.58	3.38	2.98		
DIA3008 Insulin Substudy	(N=565)	NA	(N=566)	(N=587)	(N=1153)		
Subjects with any documented hypoglycemia	208 (36.8)	NA	279 (49.3)	285 (48.6)	564 (48.9)	12.1	(7.1; 17.1)
Biochemically documented hypoglycemia[c]	208 (36.8)	NA	279 (49.3)	283 (48.2)	562 (48.7)	11.9	(6.9; 17.0)
Severe hypoglycemia	14 (2.5)	NA	10 (1.8)	16 (2.7)	26 (2.3)	-0.2	(-1.9; 1.5)
Total number of episodes	945	NA	1355	1629	2984		
Event rate per subject-year exposure	5.26	NA	7.21	8.44	7.84		
DIA3008 Sulphonylurea Substudy	(N=69)	NA	(N=74)	(N=72)	(N=146)		
Subjects with any documented hypoglycemia	4 (5.8)	NA	3 (4.1)	9 (12.5)	12 (8.2)	2.4	(-5.7; 10.6)
Biochemically documented hypoglycemia[c]	4 (5.8)	NA	3 (4.1)	9 (12.5)	12 (8.2)	2.4	(-5.7; 10.6)
Severe hypoglycemia	0	NA	0	0	0		
Total number of episodes	8	NA	14	14	28		
Event rate per subject-year exposure	0.37	NA	0.58	0.59	0.59		
DIA3015	NA	Sita (N=378)	NA	(N=377)	NA		
Subjects with any documented hypoglycemia	NA	154 (40.7)	NA	163 (43.2)	NA	2.5	(-4.8; 9.8)
Biochemically documented hypoglycemia[c]	NA	152 (40.2)	NA	162 (43.0)	NA	2.8	(-4.5; 10.1)
Severe hypoglycemia	NA	13 (3.4)	NA	15 (4.0)	NA	0.5	(-2.4; 3.5)
Total number of episodes	NA	1143	NA	1277	NA		
Event rate per subject-year exposure	NA	3.81	NA	4.14	NA		

Key: NA = Not Applicable; Sita = sitagliptin

[a] For DIA3015, the comparison is canagliflozin 300 mg minus sitagliptin

[b] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

[c] Subjects with any biochemically documented hypoglycemia episodes (symptomatic and asymptomatic); Results of LOW are included.

Cross-reference: Mod5.3.5.1\DIA3002\Table42, Mod5.3.5.1\DIA3008Insulin\Table60, Mod5.3.5.1\DIA3008SU\Table47, and Mod5.3.5.1\DIA3015\Table49

6.6.3. Summary

The analyses of hypoglycemia episodes suggests a low risk of hypoglycemia and of severe hypoglycemia in subjects treated with canagliflozin alone or in combination with other therapies

not associated with hypoglycemia. An increased incidence of hypoglycemia was observed when canagliflozin was used in combination with insulin or non-glucose dependent insulin secretagogues, which is consistent with the expected increase in hypoglycemia when an agent not associated with hypoglycemia is added to insulin or a non-glucose dependent insulin secretagogue. In study DIA3015, the comparison to an agent (sitagliptin) that has been shown not to be associated with hypoglycemia is of note—in this study, the incidence of hypoglycemia episodes overall and of severe hypoglycemia episodes was similar in the canagliflozin and sitagliptin groups (despite larger reductions in HbA_{1c} and FPG observed in the canagliflozin group, see Section 5.2.1). This suggests that the increases observed with canagliflozin appear to be comparable to other AHAs not associated with hypoglycemia when used in combination with insulin or a non-glucose dependent insulin secretagogue. The proposed labeling for canagliflozin indicates that an increased incidence of hypoglycemia was observed when canagliflozin was used in combination with insulin or a non-glucose insulin secretagogue.

6.7. Cardiovascular Safety

6.7.1. Effects on Low Density Lipoprotein-Cholesterol

Canagliflozin treatment was associated with several changes in fasting plasma lipids, including increases in HDL-C and decreases in TG, which are described in Section 5.6, and increases in LDL-C that are described in this section.

In the Placebo-controlled Studies Dataset, the placebo-subtracted LS mean absolute change from baseline for LDL-C was 4.36 mg/dL and 8.15 mg/dL, for the canagliflozin 100 mg and 300 mg groups, respectively (Table 38). The placebo-subtracted LS mean percent changes from baseline were 4.5% and 8.0%, respectively. In 52 week studies, no consistent further increases in LDL-C were observed from Weeks 26 to 52.

Table 38: LDL-C: Absolute Change From Baseline at Week 26 in the Placebo-controlled Studies Dataset

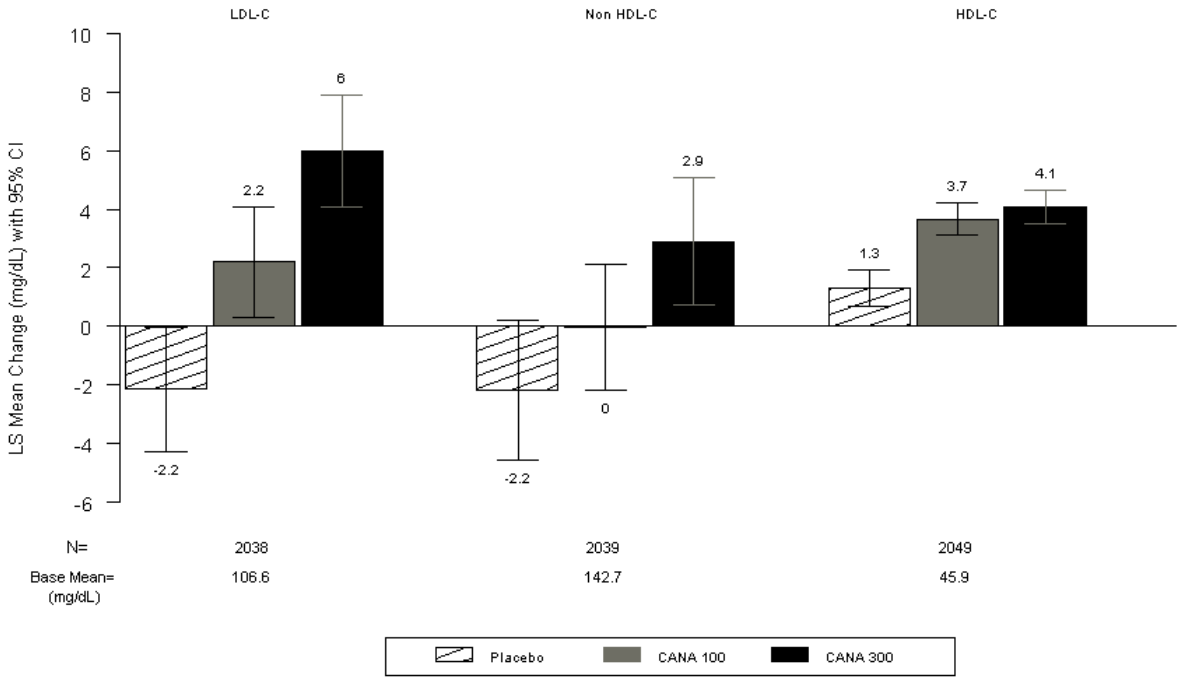
	Placebo (N=646)	CANA 100 mg (N=833)	CANA 300 mg (N=834)
Serum LDL-C (mg/dL) - fasting			
Value at Baseline			
N	562	746	730
Mean (SD)	109.5 (39.1)	106.6 (36.0)	104.4 (35.0)
Median (Range)	106.0 (21.0;252)	106.0 (14.0;233)	102.0 (16.0;227)
Value at Endpoint			
N	562	746	730
Mean (SD)	106.9 (39.1)	109.4 (36.9)	111.5 (37.1)
Median (Range)	104.0 (2.0;362)	107.0 (18.0;259)	109.0 (28.0;258)
Change from Baseline			
N	562	746	730
Mean (SD)	-2.64 (27.7)	2.79 (27.0)	7.15 (26.8)
LS Mean (SE)	-2.16 (1.1)	2.20 (1.0)	5.99 (1.0)
Median (Range)	-2.00 (-175;203)	2.00 (-104;145)	6.00 (-108;141)
Diff. of LS Means (SE)(minus Placebo)		4.36 (1.4)	8.15 (1.5)
95% CI[a]		(1.54;7.19)	(5.31;10.99)

[a] Pairwise comparison: CIs are based on the ANCOVA model with treatment, study and baseline values.
Note: Endpoint is Week 26 for all studies.
Cross-reference: tlip05a_lpac_ds1_rlip01a_cnv.rtf generated by rlip01a_cnv.sas, 22AUG2012 14:12

The placebo-subtracted LS mean percent increases from baseline in non-HDL-C in the Placebo-controlled Studies Dataset were approximately one-half as large as the increases in LDL-C (Figure 34).

In the Phase 3 studies, LDL-C levels were determined (at the central laboratory) through calculation using the Friedewald equation. To assess if these calculated values were comparable to directly measured levels (via ultracentrifugation), archived specimens (from subjects who had adequate baseline and Week 26 specimens) in Studies DIA3005 and DIA3006 were analyzed. This analysis showed generally similar LDL-C measured and calculated values (Figure 35).

Figure 34: LS Mean Absolute Change in Fasting Lipids From Baseline at Endpoint in Placebo-controlled Studies Dataset



Note: LS mean diff and 95% CI are derived via ANCOVA model including treatment, study ID and baseline value. Numbers is graph represent the LS means.

An analysis of the placebo-subtracted LS mean absolute changes in LDL-C from baseline in subgroups including by age, sex, race, BMI, eGFR, baseline statin use, and baseline LDL-C by tertile suggested that these subgroup factors had no meaningful impact on the change from baseline in LDL-C with canagliflozin. The nominal p-value for interaction between treatment and each of the subgroups was $p>0.1$.

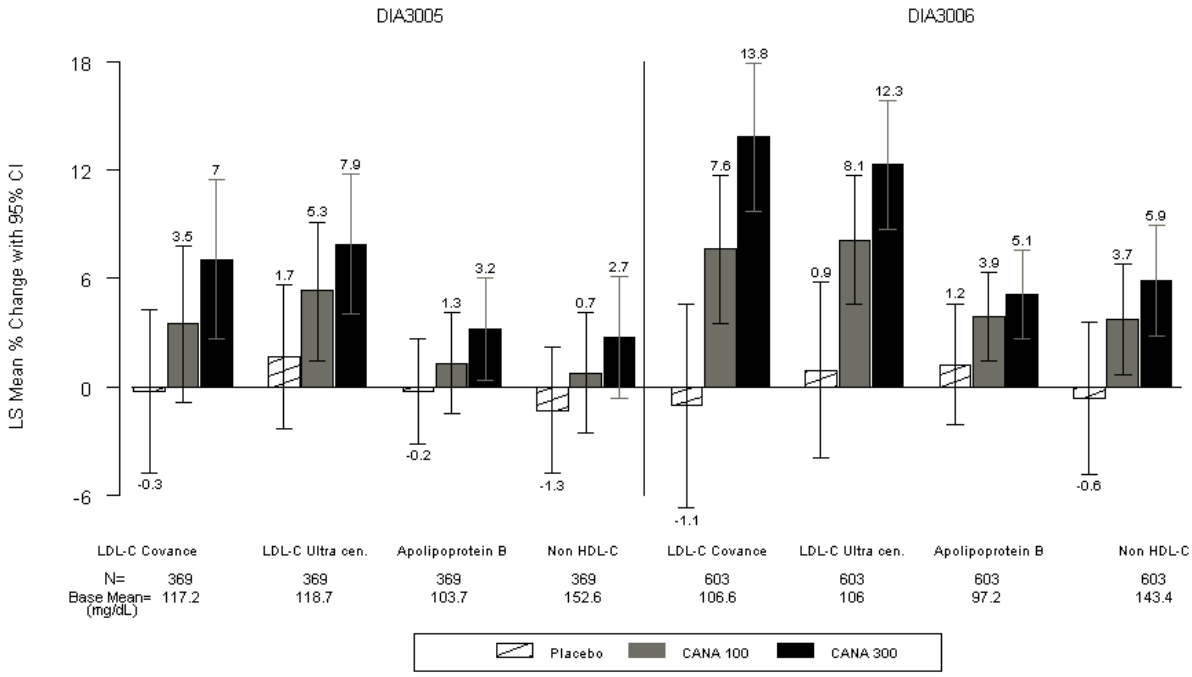
Given the increase in LDL-C, a post-hoc analysis was conducted to determine if response to statin medications was altered in subjects on canagliflozin; this examined the change in LDL-C after initiation of a statin, compared to prior values. Such an analysis is limited (post-hoc, non-randomized comparison, different duration of treatment), but suggested no substantive differences in response to statin in subjects in the canagliflozin relative to the non-canagliflozin group.

6.7.1.1. Apolipoprotein B, Non-HDL Cholesterol, LDL Particle Number

Additional measures of apolipoprotein B-containing particles were obtained: apolipoprotein B (Apo B) was measured in archived samples from two studies, the monotherapy study (DIA3005) and the add-on to metformin study (DIA3006), non-HDL-C was also analyzed in these 2 studies, and NMR assessment of particle number was assessed in the DIA3006 study. The DIA3006 study was selected based upon study size and the observation that the largest percent increase in

LDL-C was seen in this study, allowing better scope for the comparison of the change in LDL-C to Apo B. Results from these analyses are shown in Figure 35

Figure 35: Least Squares Mean Percent Changes from Baseline at Endpoint (Studies DIA3005 and DIA3006)



In both studies, the increases in Apo B and non-HDL-C were approximately half the extent of the increases in LDL-C.

As noted, archived specimens for study DIA3006 were examined using NMR spectroscopy (Liposciences, Raleigh, NC) to determine particle number and distribution. The LS mean percent change from baseline to Week 26 LOCF in the total LDL-C particle number was 5.4%, 7.2%, and 2.2% in the canagliflozin 100 mg, canagliflozin 300 mg, and placebo groups, respectively. The placebo-subtracted LS mean percent change from baseline to Week 26 LOCF in the total LDL-C particle number was 3.2% and 5.0% with canagliflozin 100 mg and 300 mg groups, respectively. In the canagliflozin 100 mg group, the increase in the total LDL-C particle number was driven primarily by an increase in particle number of the large LDL-C subfraction (placebo-subtracted increase from baseline of 41.4%) with little to no change in the small LDL-C particle number (placebo-subtracted change from baseline of -1.4%). In the canagliflozin 300 mg group, the increase in the total LDL-C particle number was driven by a large increase in the large LDL-C particle number (placebo-subtracted increase of 22.2%) and a small increase in the small LDL-C particle number (placebo-subtracted increase of 5.7%).

6.7.1.2. Overall Assessment of Lipid Changes With Canagliflozin

With regard to the clinical implications of the increase in LDL-C observed with canagliflozin, data from the Cholesterol Treatment Trialists Collaboration (Baigent 2005) suggest that a

population mean increase of 8.15 mg/dL in LDL-C for 5 years (the extent of increase observed with the canagliflozin 300 mg group) could translate into a 4% to 5% increase in the incidence of major adverse CV events over that same time period. This estimated change in CV risk assumes no change in other CV risk factors; however, canagliflozin has consistent, favorable effects on blood pressure (both systolic and diastolic). In addition, Apo B and non-HDL-C, that may be important in modulating the risk predicted by increases in LDL-C (Tabas 2007, Boekholdt 2012), were increased to a lesser extent than was LDL-C. Canagliflozin treatment leads to improvements in other endpoints such as HDL-C, body weight, and glycemic control, that have been associated with CV risk, though not established as surrogate endpoints predicting CV benefit; hence, the improvement in these factors, although beneficial, cannot necessarily be considered to counterbalance the rise in LDL-C.

Since canagliflozin has diverse effects on several established CV risk factors (increasing LDL-C, decreasing BP) and effects on other factors not clearly established as surrogate endpoints, an assessment of the potential impact on CV risk based upon the integrated changes with canagliflozin in the intermediate risk predictors (including lipids and BP) would be useful. Although a large number of risk engines have been proposed (eg, UKPDS, Framingham), both in patients with T2DM and in non-diabetic patients, none are validated and accepted as accurately predictive of subsequent CV events. Given the lack of any validated risk engine, analyses using a wide range of reported risk engines were conducted to determine the range of predicted change in risk. As shown in Attachment 21, these engines consistently showed no increase in CV risk with canagliflozin treatment. The limitations of these risk engines and the predictions with regard to changes in risk with canagliflozin must be considered: first, few include LDL-C in the model (although total cholesterol is included in most models); second, these models are largely derived from epidemiological studies, often applying baseline variables and not those on an intervention, and finally, as noted above, none are accepted as validated.

6.7.2. Cardiovascular Meta-analysis of Adjudicated Events

6.7.2.1. Analysis Methods

With reference to the December 2008 FDA guidance on evaluating CV risk in new antidiabetic therapies to treat T2DM, the sponsor developed a CV meta-analysis plan prior to the first database lock in the Phase 3 program. The analyses to establish CV safety was based on the integrated study population that included all well-controlled, randomized studies of at least 12 weeks double-blind period duration from the canagliflozin clinical program. The CANagliflozin CardioVascular Assessment Study (CANVAS; DIA3008), led by an academic Steering Committee, was a dedicated CV outcome study that contributed the majority of events towards the meta-analysis. A total of 4,330 subjects with prior CV history or risk factors for CV disease were randomized.

The primary outcome was adjudicated MACE-plus, a composite endpoint including CV death, myocardial infarction, stroke, and hospitalized unstable angina. All potential CV events were submitted to an independent adjudication committee for evaluation, and confirmed events (using criteria pre-specified in the adjudication committee charter) were included in the analysis.

Subjects not experiencing any of these CV events were censored at the last visit date or the dataset cutoff date. The CV safety composite endpoint events that occurred more than 30 days after the last dose of blinded study medication were not included in the primary analysis, but were included in a secondary sensitivity analysis. The CV risk ratio was estimated by the hazard ratio calculated for the canagliflozin group (100 mg and 300 mg groups combined) versus the control group (placebo and active comparator combined), using a stratified Cox proportional hazards model with treatment (canagliflozin and control) as the explanatory variable and study stratum (with 2 strata: CANVAS and all other well-controlled, Phase 2 and 3 randomized studies) as the stratification variable.

The CV meta-analysis to exclude a hazard ratio of 1.8 in support the US NDA filing was conducted when 201 adjudicated MACE-plus events were accumulated with a cutoff date of January 31, 2012 (from non-CANVAS Phase 3 studies unblinded by that date, and from results from CANVAS). The results of the analysis are presented in the following section. A group sequential approach, discussed below, will be applied to the analysis to exclude the CV hazard ratio of 1.3.

To control the Type 1 error, a closed testing (gatekeeping) strategy is employed. The first hypothesis, demonstrating that the CV hazard ratio of 1.8 is excluded, is a gatekeeper for the hypothesis demonstrating that the CV hazard ratio of 1.3 is excluded. The significance levels for the multiple analyses are based on the Lan DeMets spending function with an O'Brien Fleming boundary. The first analysis using an alpha of 0.001, corresponding to a 99.9% CI, was conducted at the time when the meta-analysis to rule out a hazard ratio of 1.8 was performed. The next planned interim CV meta-analysis will be conducted when approximately 500 adjudicated MACE-plus events are reached in the program; a final interim analysis (with 700 events) will be conducted if the prior interim analysis does not exclude the hazard ratio of 1.3. The alphas and the corresponding CI's to be used in these two interim analyses are presented in Table 39 below.

Table 39: Sequence of Analyses* to Exclude CV HR of 1.3

	Initial	Second	Final
Event number	201	500	700
Significance level at analysis	0.001	0.015	0.045
Confidence of the 2-sided CI	99.9%	98.5%	95.5%
Expected timing	At the time of meta-analysis for excluding CV HR ≥1.8	Approximately 2 years post-approval	Approximately 4 years post-approval

*Sequence stopped when results of analysis show that the CV HR of ≥1.3 is excluded.

6.7.2.2. Results of Cardiovascular Meta-analysis

For the prespecified, primary composite MACE-plus endpoint, the HR of the combined canagliflozin group to the non-canagliflozin group was 0.91, (95% CI: 0.68, 1.22), as indicated in Table 40. The prespecified, primary composite assessment was conducted in 95% of subjects

through the cut-off date; when excluding subjects that withdrew consent for follow-up, the assessment was conducted in 97% of subjects.

The results were highly similar by dose and consistent across subgroups. The HRs were 0.91 (95% CI: 0.65, 1.28) and 0.92 (95% CI: 0.65, 1.28) for the canagliflozin 300 mg group versus the non-canagliflozin group and for the canagliflozin 100 mg group versus the non-canagliflozin group, respectively. The results were also examined for the CANVAS (DIA3008) study and the non-CANVAS (ie, other Phase 2 and 3 studies) separately (Table 41); the HR in the CANVAS study was 1.00 and was 0.65 in the non-CANVAS studies.

Table 40: Analysis of MACE-Plus Events (Phase 2/3 Studies CV Meta-analysis)

	Non-CANA[a] N = 3327	CANA 100 mg N = 3156	CANA 300 mg N = 3149	All CANA N = 6305	Ratio (95% CI)
MACE-plus[b]					
Subjects with an event (%)	71 (2.1)	66 (2.1)	64 (2.0)	130 (2.1)	HR: 0.91 (0.68, 1.22)[c]
Number of events	74	69	66	135	
Total subject-years of exposure	3495	3480	3408	6888	
Event rate (/1,000 patient-yrs)	21.2	19.8	19.4	19.6	
Event accounting[d]					
Cardiovascular death	16 (0.5)	11 (0.3)	10 (0.3)	21 (0.3)	
Nonfatal MI	25 (0.8)	22 (0.7)	19 (0.6)	41 (0.7)	
Nonfatal stroke	12 (0.4)	22 (0.7)	20 (0.6)	42 (0.7)	
Hospitalized unstable angina	18 (0.5)	11 (0.3)	15 (0.5)	26 (0.4)	

[a] Placebo and/or active comparator therapy.
[b] Includes events that occur between the first dose of study drug and up to 30 days after discontinuation of study drug. The analysis excludes subjects in DIA3005's high glycemic cohort. Also excludes subjects in DIA3015.
[c] Hazard ratio (HR) of the combined canagliflozin group versus the non-canagliflozin group with events is from Cox proportional hazards model, stratified by DIA3008/studies other than DIA3008.
[d] Subjects with multiple event types are included in the event category that occurred earliest.
Note: mITT analysis set
Note: Inclusive of events within 30 days of last dose

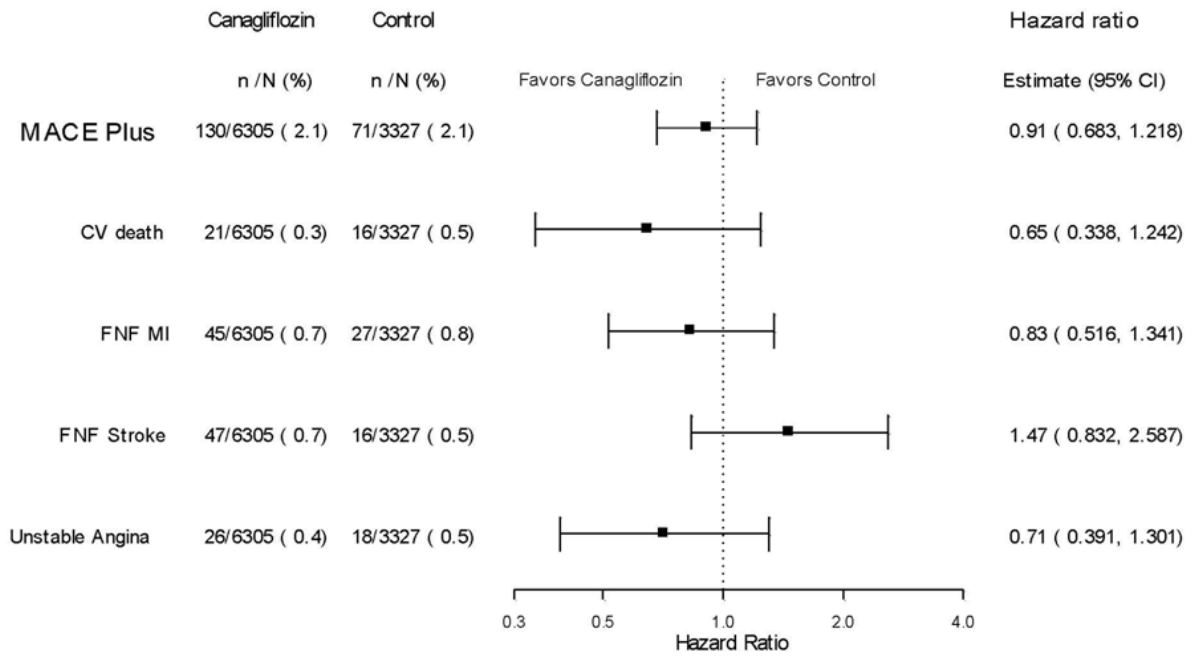
Table 41: Analysis of MACE-Plus Events: CANVAS vs non CANVAS Studies

	All Non-CANA	CANA 100 mg	CANA 300 mg	All CANA	HR (95% CI)
MACE-plus DIA3008	53/1441 (3.7%)	56/1445 (3.9%)	52/1441 (3.6%)	108/2886 (3.7%)	1.00 (0.72, 1.39)
MACE-plus non-DIA3008	18/1886 (1.0%)	10/1711 (0.6%)	12/1708 (0.7%)	22/3419 (0.6%)	0.65 (0.35, 1.21)

With respect to the components of the composite MACE-plus endpoint, as shown in Figure 36, the HRs for the combined canagliflozin group relative to the non-canagliflozin group were numerically less than 1 for all endpoints (ie, CV death, fatal/nonfatal MI, hospitalized unstable angina) except for fatal/non-fatal strokes, where the HR was 1.47, with the 95% CI around the HR including "1" (95% CI: 0.83, 2.59). Approximately 80% of the stroke events were ischemic in nature in both the canagliflozin and control groups, with the remainder not determined or hemorrhagic. With the imbalance in stroke events observed, an analysis of potentially related events, transient ischemic attacks, was conducted; there was no notable difference between

treatment groups for the incidence of adverse events of transient ischemic attacks (27 [0.4%] in the combined canagliflozin group versus 13 [0.4%] in the control group).

Figure 36: Forest Plot of Hazard Ratio for CV Components of the Primary Composite Endpoint (Phase 2/3 Studies)



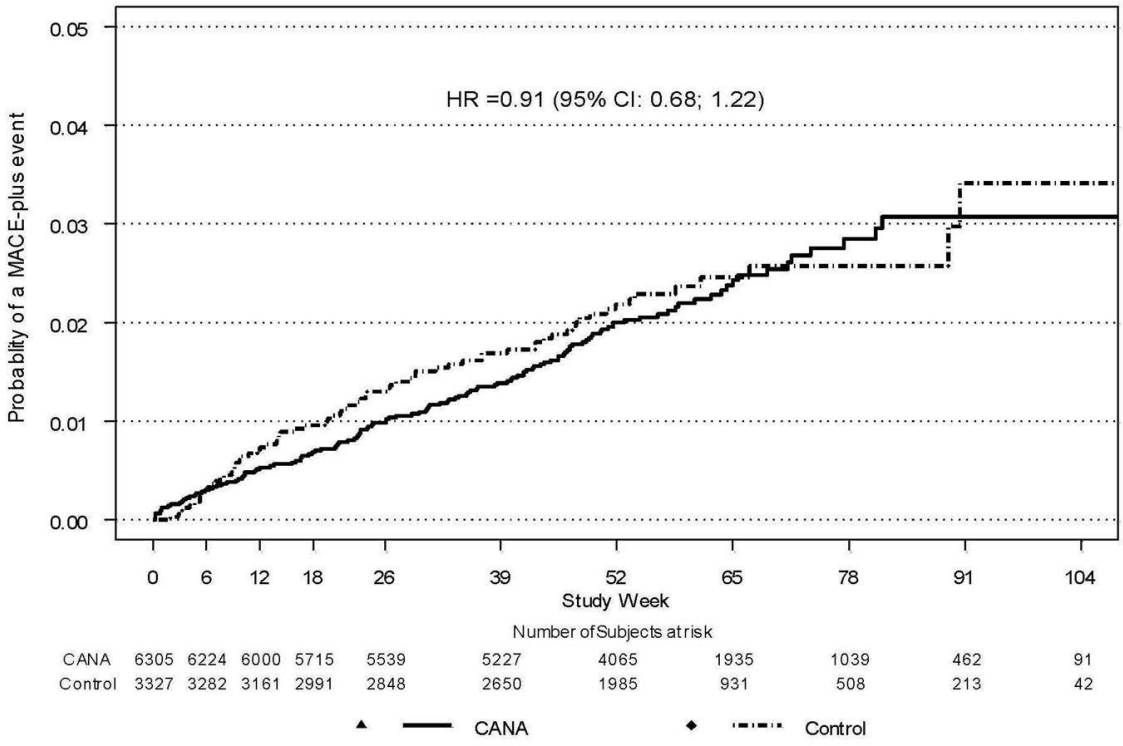
Note: In the figure above, the MI and stroke component analyses include total events (fatal and non-fatal "FNF").

An analysis of MACE-plus events including events that occurred beyond 30-days after last dose of study drug was also conducted, with results very similar to those from the primary analysis. The overall HR was 0.93 (95% CI: 0.70, 1.23), and the HR for the individual components was also similar: HR CV death was 0.80 (95% CI: 0.44, 1.47), HR for fatal or non-fatal MI was 0.82 (95% CI: 0.52, 1.31), HR for fatal or non-fatal stroke was 1.48 (95% CI: 0.84, 2.62), and the HR for unstable angina was 0.76 (95% CI: 0.43, 1.36).

Examination of the Kaplan-Meier curve for MACE-plus endpoint (Figure 37) showed that there was a modestly higher rate of events in the canagliflozin groups relative to the non-canagliflozin groups occurring in the first 30 days after randomization (15 events in the total canagliflozin group vs 5 in non-canagliflozin group; with 2:1 randomization ratio, canagliflozin to non-canagliflozin) in the overall CV meta-analysis; this was more prominent in the DIA3008 study (13 events in the canagliflozin groups relative to the 1 placebo event), with the opposite pattern in the non-DIA3008 studies (2 events in the canagliflozin group relative to 4 events in the non-canagliflozin group). On the other hand, in the next 30 day period in the DIA3008 study (Days 31 to 60), a higher rate of events was observed in the placebo group: 5 events in the combined canagliflozin groups, and 8 events in the placebo group, with a similarly higher rate in the subsequent 30 day period (ie, Days 61 to 90) in this study in the placebo group. Since the incidence of adverse events related to reduced intravascular volume most prominently increased

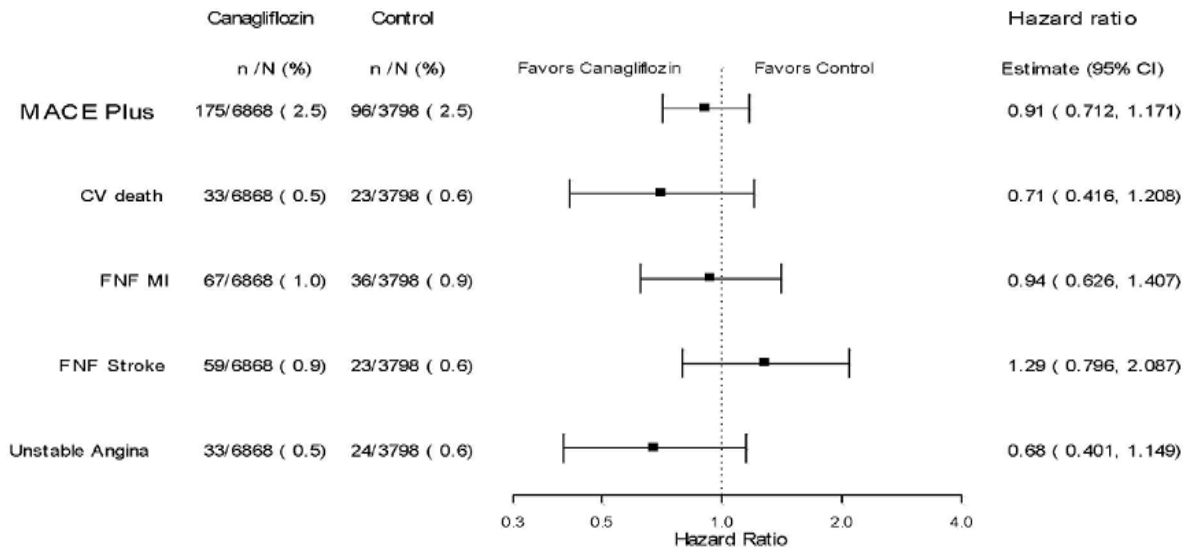
over the first 12 weeks post-randomization (see Figure 26), the higher incidence of CV events in CANVAS within the first 30 days, and then lower incidence over the subsequent 60 days, would not suggest a relationship to reduced intravascular volume. Overall, marked month-to-month variability in the estimate monthly hazard rates was seen suggesting that the imbalance observed in the first month in DIA3008 likely reflects a chance occurrence.

Figure 37: Kaplan-Meier Plot of Time to the First Treatment-Emergent MACE-Plus events (Phase 2 Studies and Phase 3 to January 31, 2012)



The European Medicines Agency requested an updated assessment of new stroke events (i.e., an update to the stroke results from the 31 January 2012 CV meta-analysis); the updated analysis has been completed, and was also submitted to the FDA. The updated CV meta-analysis included all adjudicated stroke events through 20 November 2012 and includes data from 2 additional studies (DIA2003 and DIA3015) which were ongoing and blinded at the time of the original (31 January 2012) CV meta-analysis. The updated analysis (20 Nov 2012) (Figure 38) shows that the point estimate of the hazard ratio for MACE-plus is consistent with the original meta-analysis. A lower hazard ratio for fatal and non-fatal strokes (1.29 with a 95% CI of 0.8 to 2.09) was observed relative to the hazard ratio observed in the initial CV meta-analysis (1.47).

Figure 38: Forest Plot of Hazard Ratio for CV Components of the Primary Composite Endpoint (Phase 2/3 Studies) – 20-November-2012 cut-off



6.7.2.3. Summary of Cardiovascular Safety

The CV safety of canagliflozin was assessed in a broad population of subjects with T2DM across the Phase 2 and 3 clinical development program. This program included subjects at higher CV risk, and assessed CV events in a standardized manner using an independent and blinded CV endpoint adjudication committee. Three of the 4 components of the MACE-plus composite endpoint had estimated HRs that were < 1.0, and one, fatal-non-fatal stroke, had an estimated HR that was above 1.0, with the 95% CIs around these component HR including 1.0. Overall, these analyses (the analysis conducted on results through 31 January 2012, and the recent updated analysis on results through 20 November 2012) suggest that treatment with canagliflozin is not associated with an increased occurrence of CV events, and meets the FDA guidance requirement (demonstrating that the upper bound of the CI is < 1.8) for NDA filing.

6.8. Venous Thromboembolic Events

There was no preclinical signal for increased thrombotic potential with canagliflozin and no deep venous thrombosis or pulmonary embolic adverse events were reported in the Phase 1 or 2 studies. The FDA requested that in all SGLT clinical development programs, venous thromboembolic (VTE) events be adjudicated and analyzed consistent with this, all potential VTE events (ie, possible deep venous thrombosis or pulmonary embolic events) across the Phase 3 program were submitted for adjudication to the CV endpoint adjudication committee.

In Table 42, adjudicated events of VTE demonstrate no notable imbalance between the canagliflozin and non-canagliflozin groups.

Table 42: Venous Thromboembolic Adverse Events in Broad Dataset (through 01 July 2012)

Dictionary-Derived Term	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)	All Non-CANA Minus ---All CANA --- 95%CI[a]
Total no. subjects with venous thromboembolic adverse events	6 (0.2)	6 (0.2)	8 (0.3)	14 (0.2)	(-0.3; 0.2)
Incidence rate per 1000 subject-years exposure (SE)[b]	1.49 (0.67)	1.47 (0.66)	2.01 (0.76)	1.74 (0.48)	(-1.37; 1.86)
Deep vein thrombosis	4 (0.1)	3 (0.1)	3 (0.1)	6 (0.1)	(-0.2; 0.1)
Pulmonary embolism	2 (0.1)	3 (0.1)	5 (0.2)	8 (0.1)	(-0.1; 0.2)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

[b] Exposure adjusted incidence rates are per 1000 subject-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total subject-year exposure for all safety subjects in each treatment group). SE denotes the standard error of the incidence rates defined as incidence rate divided by the square root of the total number of subjects with the adverse event - 1.

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence Is based on the number of subjects experiencing at least one adverse event, not the number of events, regardless of use of rescue medication.

Note: These events underwent independent assessment for adjudication.

Note: The events are identified by (1) adjudicated vein thrombosis cases, (2) adjudicated cardiac death cases with either 'Pulmonary thromboembolism' or 'Pulmonary embolism' as the proximate cause.

Cross-reference: 4MSU Table 44; tae64vtecin0401jul12raevte2ir.rtf generated by raevte2ir.sas, 18SEP2012 13:09

Of the 20 subjects reported to have VTE in the Broad Dataset up through 01 July 2012, 2 subjects, both in the canagliflozin 300 mg group, experienced the event in the first month post-randomization. Neither of the 2 subjects with adverse events of VTE was reported to have an event of reduced intravascular volume prior to VTE.

Based upon these data, it is concluded that canagliflozin is not associated with an increased risk of VTE events.

6.9. Malignancies Monitored in the Phase 3 Clinical Program

In Section 2, findings in the canagliflozin 2-year rat carcinogenicity study are described (an increase in LCTs, pheochromocytomas, and renal tubular cell tumors). As discussed in that section, the mechanistic toxicology program showed that the increase in LCTs was related to increased LH seen in canagliflozin-treated rats (an increase in LH is a well established mechanism of tumorigenesis in the rat); this rise in LH is not seen in clinical studies. The increase in pheochromocytomas and RTTs was shown to be related to the induction of carbohydrate malabsorption and its metabolic consequences (canagliflozin does not induce carbohydrate malabsorption in humans). Thus, an extensive mechanistic toxicology program demonstrated that the findings in rats were not relevant for human risk; nonetheless, across the Phase 3 clinical program, careful assessment of the occurrence of these tumors was conducted. In addition, reports from the dapagliflozin, another SGLT2 inhibitor, showed a numerical imbalance in the occurrence of breast and bladder cancer events

(Dapagliflozin FDA Briefing Book); hence, the occurrence of these 2 tumor types were also carefully monitored in the clinical studies for canagliflozin.

Table 43 shows the incidences of bladder cancer, breast cancer, and renal cancer adverse events. These tumor adverse events occurred at a low and similar incidence across treatment groups. Percent incidence of breast cancer is calculated based on the number of female subjects in each group. No breast cancer events were reported among male subjects. Note that there were no events of pheochromocytoma or LCTs reported. The analysis of the incidence of these tumor types was updated to include all data through 15 November 2012, based upon a request from the FDA.

Table 43: Post Randomization Bladder, Breast, and Renal Cancer Adverse Events in Phase 3 Program(to 15 November 2012)

Grouped Term	All Non-CANA n (%)	CANA 100 mg n (%)	CANA 300 mg n (%)	All CANA n (%)
Bladder cancer				
N	3640	3139	3506	6645
Number subjects with adverse events[a]	4 (0.11)	2 (0.06)	3 (0.08)	5 (0.07)
Incidence rate per 1000 subject-years exposure	0.84	0.44	0.63	0.53
Breast cancer				
N	1501	1313	1514	2827
Number subjects with adverse events[b]	6 (0.39)	5 (0.37)	7 (0.45)	12 (0.41)
Incidence rate per 1000 subject-years exposure	3.05	2.61	3.39	3.01
Renal cell cancer				
N	3640	3139	3506	6645
Number subjects with adverse events[c]	3 (0.08)	2 (0.06)	3 (0.08)	5 (0.07)
Incidence rate per 1000 subject-years exposure	0.63	0.44	0.63	0.53

[a] Selected bladder cancer adverse events are based upon a prespecified list of preferred terms from a MedDRA query listed in the SAP

[b] Selected breast cancer adverse events are based upon a prespecified list of preferred terms from a MedDRA query listed in the SAP (narrow list).

[c] Selected renal cancer adverse events are based upon a prespecified list of preferred terms from a MedDRA query listed in the SAP (narrow list) with the addition of the term 'Renal neoplasm' (broad list).

Note: Percentages calculated with number of subjects in each group as denominator.
Note Approximate Exposure adjusted incidence rates are per 1000 subject-years and calculated as 1000*(the total number of subjects with at least one specified event divided by the total subject-year exposure for all safety subjects in each treatment group). Includes all P3studies (including subjects from DIA3015 and subjects in high glycemic cohort of DIA3005) through 15 Nov 2012

In summary, few events of breast, bladder, or renal cancer and no events of pheochromocytoma or LCTs were reported in the Phase 3 clinical program. There was no meaningful imbalance in the events of breast, bladder, and renal cancers.

6.10. Hepatic Safety

There was no meaningful preclinical toxicology signal for liver injury. However, since hepatic safety is a significant issue in drug development, this was carefully assessed throughout the clinical development program for canagliflozin.

In Phase 3 studies, hepatic safety of canagliflozin was assessed by examining mean changes in liver function tests, assessing the incidence of events of increased ALT, AST, or bilirubin (or combined ALT/AST and bilirubin) meeting pre-specified change criteria, and by adjudication of events meeting criteria for potentially important hepatotoxicity.

In the Phase 2 and 3 clinical studies, a consistent decrease was observed in the mean change from baseline in ALT, aspartate aminotransferase (AST), and GGT, with smaller decreases observed for alkaline phosphatase (see Section 6.12.1; Table 47).

With regard to the incidence of events of ALT elevations (Table 44), there was no discernible imbalance for events >3x ULN (either "any" or "last available" value) in the canagliflozin compared to non-canagliflozin groups. There was a greater incidence of events >5x (and higher cutpoints) in the canagliflozin 100 mg group, with no notable difference in the incidences in the canagliflozin 300 mg and non-canagliflozin groups (and with the 95% CI around the between-group difference for the combined canagliflozin group relative to the non-canagliflozin group including "0"); all events of >5x ULN were submitted for adjudication, as discussed below.

Table 44: Number of Subjects with Serum Alanine Aminotransferase Elevations in Broad Dataset (through 01 July 2012)

Parameter Time Interval Pre-Defined Limits Of Change	All Non-CANA n (%)	CANA 100 mg n (%)	CANA 300 mg n (%)	All CANA n (%)	All CANA Minus -- All Non-CANA - Diff(%)	 95%CI[a]
Serum Alanine Aminotransferase (U/L)						
ANY POSTBASELINE VALUE	3163	3019	2970	5989		
ALT > 3x ULN	24 (0.8)	28 (0.9)	21 (0.7)	49 (0.8)	0.1	(-0.3; 0.5)
ALT > 5x ULN	6 (0.2)	13 (0.4)	8 (0.3)	21 (0.4)	0.2	(-0.1; 0.4)
ALT > 8x ULN	2 (0.1)	7 (0.2)	2 (0.1)	9 (0.2)	0.1	(-0.1; 0.2)
ALT > 10x ULN	2 (0.1)	4 (0.1)	2 (0.1)	6 (0.1)	0.0	(-0.1; 0.2)
ALT > 20x ULN	0	1 (<0.1)	2 (0.1)	3 (0.1)	0.1	(-0.0; 0.1)
ALT > 3x ULN and Bilirubin > 2x ULN	0	1 (<0.1)	2 (0.1)	3 (0.1)	0.1	(-0.0; 0.1)
Incidence rate per 1,000 subject-years exposure of ALT > 3 x ULN	*5.97*	*6.88*	*5.28*	*6.09*		
LAST POSTBASELINE VALUE	3163	3019	2970	5989		
ALT > 3 x ULN	11 (0.3)	11 (0.4)	8 (0.3)	19 (0.3)	-0.0	(-0.3; 0.2)
ALT > 5 x ULN	4 (0.1)	8 (0.3)	5 (0.2)	13 (0.2)	0.1	(-0.1; 0.3)
ALT > 8 x ULN	0	4 (0.1)	2 (0.1)	6 (0.1)	0.1	(-0.0; 0.2)

[a] CI for pairwise comparison using normal approximation for the difference in rates or for the difference in proportions with a continuity correction.

Note: ALT >3X ULN and Serum Bilirubin >2X ULN is composite criterion with the Serum Bilirubin elevation >2 X ULN within 30 days following the ALT elevation >3x ULN.

Note: Exposure adjusted incidence rates are per 1,000 subject-years and calculated as 1,000*(the total number of subjects with an elevation divided by the total subject-year exposure for all treated subjects who have a postbaseline lab value)

Cross-reference: 4MSU attachments DLAB23ALT_04_01JUL12 and DLAB02B_04_01JUL12

A Hepatic Events Adjudication Committee (HEAC) was organized to assess (blinded to treatment group assignment) all events in the sponsor's clinical program meeting any one of the following adjudication criteria:

- ALT or AST elevations ≥ 5x ULN, or
- Combined ALT or AST ≥3x ULN and total bilirubin ≥2x ULN, or
- Any adverse events corresponding to a list of selected / pre-specified liver injury-related preferred terms

To identify such events, elevations in measurements from the central laboratory meeting one of these criteria, or tests reported from local laboratories meeting one of these criteria (ie, in narratives from adverse event reports) were included (leading to the greater number of events reported in Table 45 [all events meeting criteria] relative to Table 44 [abnormalities meeting criteria from central laboratory measurements]). Overall, 48 events (Table 45) in the combined canagliflozin group met one or more of these criteria (including 42 meeting ALT or AST or combined criteria, and 6 with an adverse event term meeting criteria).

Laboratory data, case report forms, patient profiles, discharge summaries, diagnostic tests, other relevant case information and a narrative written by the sponsor were provided to each of the external experts. Each external expert evaluated the case for type and severity of liver injury, causality with regard to study drug, and for alternative etiology(-ies). Responses were collated by the sponsor. Causality with regard to study drug was classified into one of 5 categories (definite, probable, possible, unlikely, or excluded). Agreement between all 3 external experts for assessment of causality (ie, agreement within one causality category) was required; a teleconference was convened for the 3 external experts (with no sponsor participation) if consensus was not obtained by initial individual reviews of a case, during which the case was discussed and a final causality assessment determined and provided to the sponsor. Adjudication results with regard to causality category are presented by individual category (ie, definite, probable, etc) and also grouped into "potentially-related" (combining definite, probable, or possible categories), "likely-related" (combining definite and probable categories), or "unrelated" (combining unlikely and excluded categories). As noted, all assessments by HEAC members and consensus meetings were conducted independently, with no participation by sponsor personnel.

There were no notable differences between treatment groups for the incidence of events considered as potentially-associated with study drug (definite, probable, or possible categories), with 6 events (0.08%) and 4 events (0.10%) in the combined canagliflozin and non-canagliflozin groups, respectively. No event in either canagliflozin group was considered as definite or probable (all 6 events potentially-related assessed as "possible").

An imbalance was seen for events meeting combined criteria (ie, ALT or AST >3xULN and bilirubin >2xULN), with a distribution of 10 events (0.14%) and 2 events (0.05%) in the combined canagliflozin and non-canagliflozin groups, respectively (Table 45). The

HEAC-determined causality for all of the events in the combined canagliflozin group was either unlikely (N=3) or excluded (N=7) in relation to study drug, since all of these events had alternative etiologies defined. These combined criteria events, therefore, did not meet Hy's Law criteria (which includes no alternate etiology) (FDA 2009).

Table 45: HEAC Causality Assessment for the Cases Submitted for Adjudication Sent for HEAC Review

HEAC Criteria Causality	Non-Cana n/N (%)	Cana 100 mg n/N (%)	Cana 300 mg n/N (%)	All Cana n/N (%)
Any of the 3 Laboratory Criteria:				
Number of Cases	13	23	19	42
Definite or Probable	1/3952(0.03)	0	0	0
Definite, Probable or Possible	4/3952(0.10)	4/3342(0.12)	2/3715(0.05)	6/7348(0.08)
ALT ≥5xULN				
Number of Cases	12	19	15	34
Definite or Probable	1/3952(0.03)	0	0	0
Definite, Probable or Possible	4/3952(0.10)	4/3342(0.12)	1/3715(0.03)	5/7348(0.07)
AST ≥5xULN				
Number of Cases	7	13	13	26
Definite or Probable	1/3952(0.03)	0	0	0
Definite, Probable or Possible	3/3952(0.08)	1/3342(0.03)	2/3715(0.05)	3/7348(0.04)
ALT or AST ≥3xULN followed by total bilirubin ≥2xULN within 30 days of rise of ALT or AST				
Number of Cases	2	6	4	10
Definite or Probable	0	0	0	0
Definite, Probable or Possible	0	0	0	0
Other[a]				
Number of Cases	1	4	2	6
Definite or Probable	0	0	0	0
Definite, Probable or Possible	0	0	0	0

[a] Based on a search of pre-specified selected AE preferred terms suggesting potential hepatic injury event

Note: A total of 4 subjects with adjudicated events were from Phase 1 or non-controlled studies and hence are not included in this table; all subjects met ALT or AST criteria (ie, ≥5xULN), and none were adjudicated as definite, probable, or possible (attachment LHEAC04_01JUL12).

Note: N is the total number of subjects from Phase 3 studies: DIA3002, DIA3004, DIA3005 (main study), DIA3006, DIA3008, DIA3009, DIA3010, DIA3012 and DIA3015 and Phase 2 studies: DIA2001, OBE2001 and DIA2003, events for the hepatic adjudication in these studies up to July 1 2012 were included.

Note: Hepatic Event Assessment Committee (HEAC) consisted of 3 hepatologists who provided independent assessments for each case.

Note: "Number of Cases" is the number of cases meeting the HEAC criteria classification.

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Brief narratives of the 3 subjects considered as unlikely but not excluded follows. Table 46 provides the alternative etiologies in subjects adjudicated as "excluded or unlikely":

- Subject 803972: This 61-year-old man, randomized to canagliflozin 100 mg, met liver criteria for ALT and AST >5x ULN on Day 281 with ALT 251 U/L (normal range: 6-43 U/L) and AST 207 U/L (normal range: 11-36 U/L). The subject's total bilirubin (TB) remained within normal limits. An abdominal and pelvic ultrasound on Day 7 showed

hepatomegaly and a small hypoechoic lesion on the right lobe. On Day 260, another abdominal ultrasound showed a complex cystic space occupying lesion on the left liver lobe and prostatic enlargement. On Day 281, liver serology results indicated a positive result for Hepatitis E IgM antibody, indicating an acute infection. Treatment with study drug was discontinued on Day 284. Other serology tests indicated the subject was positive for CMV IgG, EBV Ab VCA IgG and total HAV antibody. The subject's LFT results were within normal or near normal limits on Day 456. The HEAC adjudicated the case with a causality assessment of unlikely with an alternative etiology of HEV infection.

- Subject 804055: This 66-year-old man, randomized to canagliflozin 100 mg, met liver criteria for ALT >3x ULN and TB >2x ULN on Day 329 with ALT 113 U/L (normal range: 9-33 U/L) and TB 2.6 mg/dL (normal range: 0.1-1.0 mg/dL). Treatment with study drug was discontinued on Day 239 and LFTs on that day revealed ALT of 77 U/L and TB of 8.6 mg/dL. A MRI scan performed on Day 327 showed no biliary dilation, possible cholangitis, and bilateral renal cysts. Serology tests for hepatitis were negative. Other serology tests indicated the subject was positive for CMV IgG and EBV Ab VCA IgG. On Day 338, an ultrasound needle liver biopsy indicated prominent proliferative duct reaction with cholestasis and portal fibrosis. Liver enzyme values decreased through Day 412 but remained elevated (ALT 85 U/L and TB 2.7 mg/dL). Follow-up information obtained from the investigator with an additional MRI on Day 448 and an ERCP on day 475 suggest a likely diagnosis of primary sclerosing cholangitis. The HEAC adjudicated the case with a causality assessment of unlikely with an alternative etiology of cholangitis.
- Subject 902009: This 72-year-old man, randomized to canagliflozin 100 mg, met liver criteria for ALT and AST >5x ULN and TB >2x ULN on Day 392 with ALT 962 U/L (normal range: 6-32 U/L), AST 1052+ U/L (normal range: 9-34 U/L) and TB 2.5 mg/dL (normal range: 0.2-1.2 mg/dL). The subject's ALP and GGT were also elevated at 153 (normal range: 35-123) and 604 U/L (normal range: 5-50 U/L), respectively. LFTs for this subject were within normal limits through Day 357, except for a very slight elevation in ALT and AST noted on Day 259. On Day 396, LFTs were within normal range, with values similar to prior results. The subject experienced food poisoning on Day 390 which was treated with activated charcoal, hepabene and pancreatin. The subject continued study drug throughout this time without interruption. It is suspected that a blood sample may have been inadvertently switched with another subject's sample (Subject 900990) at the same site. Both subjects had visits at the site on the same day; the day this subject met liver criteria. The HEAC adjudicated the case with a causality assessment of unlikely due to likely sampling error.

Despite the imbalance in combined criteria events submitted for adjudication, other causes were well established in all canagliflozin treated subjects, with obstructive causes (cholecystitis, cholelithiasis) among the most common alternative etiologies.

Table 46: HEAC Causality Assessment and Alternative Etiology of the Cases Meeting Adjudication Criteria of ALT or AST ≥3xULN and Total Bilirubin ≥2xULN Within 30 Days of Rise of ALT or AST

Subject Number	Treatment group	Final Review Assessment	Alternative Etiology
100516	Cana 300mg	EXCLUDED	Cholecystitis, atypical chronology
120205	Cana 100mg	EXCLUDED	Cholelithiasis with cholecystitis and choledocholithiasis
150565	Cana 300mg	EXCLUDED	choledocholithiasis
400373	Cana 100mg	EXCLUDED	Gallstone disease
801838	Placebo	EXCLUDED	Sepsis, portal vein thrombosis and hepatic infarction
803577	Cana 300mg	EXCLUDED	Cholangiocarcinoma
803972	Cana 100mg	UNLIKELY	See Narrative
804055	Cana 100mg	UNLIKELY	See Narrative
804977	Cana 300mg	EXCLUDED	Obstructive jaundice: adenocarcinoma
805552	Cana 100mg	EXCLUDED	Cholelithiasis with acute cholecystitis
901651	Glimepiride	EXCLUDED	No temporal relation to study treatment
902009	Cana 100mg	UNLIKELY	See Narrative

In summary, the results of hepatic safety evaluations, including mean changes, incidences of marked laboratory abnormalities, and adjudication of events meeting pre-specified criteria, support the hepatic safety of canagliflozin.

6.11. Photosensitivity

Based upon preclinical findings, Phase 1 clinical photosensitivity studies were conducted. These studies showed no evidence of delayed photosensitivity reactions (the usual basis for clinically important photosensitivity, comparable to a sunburn-type reaction) in the canagliflozin 100 mg or 300 mg groups. An immediate phototoxicity response (localized edema and pruritus) was observed at doses of 300 mg and above. The standard approach in Phase 1 photosensitivity studies is the delivery of the dose of irradiance at approximately 30-fold the most intense irradiance of natural sunlight or typical tanning bed exposure. The signal for an increase in the occurrence of an immediate phototoxicity response was investigated by 2 additional Phase 1 studies that showed that the immediate response was markedly attenuated or avoided when the dose or irradiance was reduced to 3-fold above the most intense irradiance of natural sunlight or typical tanning bed exposure. This suggested that the finding of the immediate phototoxicity response in the Phase 1 clinical photosensitivity study was unlikely to be of clinical relevance. Nonetheless, in Phase 3 studies, this issue was carefully assessed, using the Phase 3 Broad Dataset with the cutoff date as of 01 July 2012.

In the canagliflozin Phase 3 studies (with the exception of DIA3009), the protocol did not provide specific instructions to be given to the subjects regarding the use of photoprotection (advice for photoprotection was at the investigator's discretion based upon usual practice). The incidence of photosensitivity-related adverse events was low, with a modest imbalance that was non-dose-related (unlike the observations in the Phase 1 study) in the combined canagliflozin group relative to the non-canagliflozin group. The specific adverse event of photosensitivity reaction occurred with a low incidence in the canagliflozin 100 mg (0.2%) and 300 mg (0.2%) groups and the non-canagliflozin group (0.1%). The events reported across treatment groups were generally mild in intensity and without a severe or serious clinical event occurring to suggest a clinically important photosensitivity reaction. Overall, the lack of dose-dependence makes the relationship to study drug unlikely.

6.12. Laboratory Changes With Canagliflozin

Assessment of clinical laboratory analytes included evaluation of mean (and median) changes over time, and the proportion of subjects meeting pre-specified change criteria. The primary assessment of mean changes over time is based upon the Placebo-controlled Studies Dataset.

6.12.1. Chemistry Analytes: Liver Function Tests

Mean percent changes from baseline to Week 26 for selected liver function test values are provided in Table 47.

For ALT, moderate mean percent reductions from baseline were observed at Week 26 in the canagliflozin 100 mg and 300 mg groups (-7.5% and -11.1%, respectively), with a small increase (2.7%) observed in the placebo group. Relative to the reductions in ALT, smaller decreases from baseline in the canagliflozin groups were seen for AST and alkaline phosphatase. Moderate reductions from baseline in GGT, similar in magnitude to the reductions observed for ALT, were seen in the canagliflozin groups. For serum bilirubin, mean percent increases of 8.1% and 9.2% were observed in the canagliflozin 100 mg and 300 mg groups, respectively, compared with 2.3% in the placebo group. In Phase 1 studies, increases in bilirubin with single doses of canagliflozin were observed; in Phase 3 studies, a rise in serum bilirubin was seen at the first measurement (Week 6), and then remained stable. There was no notable increase in the proportion of subjects meeting pre-specified change criteria for increases in serum bilirubin (>ULN and >25% increase from baseline), and no events of increases in serum bilirubin meeting pre-specified change criteria associated with elevations in ALT or AST (other than infrequent events, described in Section 6.10, above, none of which were considered as related to study drug based upon adjudication). The small increase in bilirubin, occurring even after single doses of canagliflozin, and unassociated with other alterations of liver function tests, suggest a minor transporter interaction as the likely mechanism. The small stable mean increase in bilirubin, in concert with broad improvements in other liver function tests, does not suggest clinical relevance.

Table 47: Selected Liver Function Test Values: Mean and Mean Percent Change From Baseline at Week 26 in Placebo-controlled Studies Dataset

	Placebo	CANA 100 mg	CANA 300 mg	All CANA
Serum Alanine Aminotransferase (U/L)				
N	N	N	N	N
Mean baseline	522	711	714	1425
Mean % change (SD)	28.1	27.8	28.5	28.2
Median % change	2.7 (41.2)	-7.5 (33.9)	-11.1 (34.5)	-9.3 (34.3)
Serum Alkaline Phosphatase (U/L)				
N	526	715	718	1433
Mean baseline	77.9	76.7	77.0	76.8
Mean % change (SD)	-0.0 (15.0)	-0.8 (15.3)	-3.1 (15.6)	-1.9 (15.5)
Median % change	-1.9	-2.4	-4.1	-3.3
Serum Aspartate Aminotransferase (U/L)				
N	517	703	710	1413
Mean baseline	23.3	22.9	23.4	23.2
Mean % change (SD)	4.9 (41.4)	-2.9 (26.8)	-3.6 (30.2)	-3.3 (28.5)
Median % change	0.0	-5.6	-5.9	-5.9
Serum Bilirubin (umol/L)				
N	523	713	717	1430
Mean baseline	0.53	0.51	0.51	0.51
Mean % change (SD)	2.3 (34.8)	8.1 (38.2)	9.2 (41.6)	8.7 (39.9)
Median % change	0.0	0.0	0.0	0.0
Serum Gamma Glutamyl Transferase (U/L)				
N	526	715	718	1433
Mean baseline	40.7	36.8	39.7	38.3
Mean % change (SD)	4.3 (59.8)	-7.4 (35.2)	-11.5 (39.4)	-9.5 (37.4)
Median % change	-3.5	-11.0	-14.3	-12.5

Note: For each measurement, only the subjects who had both baseline and postbaseline measurements are included.
Cross-reference: ISS attachment DLAB01FF_01

6.12.2. Chemistry Analytes: Electrolytes

No meaningful changes from baseline were seen for sodium, chloride, bicarbonate, or calcium in either the Placebo-controlled Studies Dataset or in subjects with renal impairment (DIA3004). There were also no meaningful increases in events meeting prespecified change criteria for these analytes. Small increases in serum phosphate and magnesium are discussed in Section 6.5.2.

In the Broad Dataset through 01 July 2012, there was no discernible mean change from baseline in potassium. An increase in the occurrence of episodes of elevated serum potassium values meeting pre-specified change criteria (greater than 5.4 mEq/L [5.4 mmol/L] and 15% above baseline) any time during the double-blind treatment period was seen in 7.1% of subjects in the canagliflozin 100 mg group, 9.0% of subjects in the canagliflozin 300 mg group, and 7.2% of subjects in the non-canagliflozin group. Among subjects with episodes of increases in potassium, the majority of subjects had potassium levels that were <6 mEq/L. In the Pooled Renal Impairment Dataset, incidences of elevated serum potassium meeting the prespecified change criteria were 7.2% with the canagliflozin 100 mg group, 12.0% with the canagliflozin 300 mg group, and 7.9% with the placebo group. In general, elevations were transient and did not require

specific treatment. More severe elevations were rare and were generally seen in subjects with renal impairment, with baseline elevated potassium concentrations and/or who were on multiple medications that reduce potassium excretion, such as potassium-sparing diuretics and ACE inhibitors.

6.12.3. Chemistry Analytes: Serum Urate

Moderate decreases in the mean percent change from baseline in serum urate were observed at Week 26 in the canagliflozin 100 mg and 300 mg groups (-10.1% and -10.6%, respectively) compared with placebo, where a slight increase from baseline (1.9%) was observed. Decreases in serum urate in the canagliflozin groups were maximal or near maximal by Week 6.

In Phase 1 studies, decreases in serum uric acid were seen within days of initiating canagliflozin treatment and in Phase 3 studies were maintained for up to at least 52 weeks of treatment with canagliflozin. This reduction in serum uric acid was related to an increase in fractional and a transient increase in 24 hour urine urate excretion (with the increase in 24-hour excretion returning to baseline as serum uric acid levels decreased). The transient increase in urinary urate excretion was not associated with an increase in adverse events of nephrolithiasis in the Broad Dataset.

6.12.4. Hematology Analytes: Hemoglobin

Across datasets, a modest increase in hemoglobin concentration (with commensurate increases in hematocrit and erythrocyte count) was observed. This rise likely reflects the diuretic effect of canagliflozin, with a reduction in plasma volume. In the Phase 2b study in obese and overweight non-diabetic subjects, reticulocyte counts were measured every 3 weeks over the 12 week double-blind treatment period; a small and transient increase was seen, observed at Week 3 and no longer present at later time points. In the Phase 2b study in subjects with T2DM, reticulocyte counts were measured at Weeks 6 and 12, and no increase in reticulocytes was observed. This may suggest a transient modestly increased red cell production (that may reflect the reduction in plasma volume with transient decreased renal perfusion), but also indicates that the extent of this effect would likely be only a small contributor to increased hemoglobin, with hemoconcentration likely the main component.

In the Placebo-controlled Studies Dataset, at Week 26, mean changes from baseline with the canagliflozin 100 mg and 300 mg groups were 3.5% and 3.8%, respectively, and -1.1% in the placebo group; this mean increase was associated with an increase in the proportion of subjects meeting prespecified change criteria (≥2.0 mg/dL increase from baseline): 6.0% and 5.5% in the canagliflozin 100 mg and 300 mg groups, respectively, and 1.0% in the placebo group. For most subjects, the value meeting the pre-specified change criteria remained within the normal range for hemoglobin. Comparable increases were seen in subjects with renal impairment (in DIA3004) and in older subjects (in DIA3010), and over a longer treatment period (DIA3009). The increases were observed at the initial determination (at Week 6 in most studies) and then remained generally stable over the double-blind treatment period. These changes in hemoglobin are unlikely to be of clinical relevance.

7. Continuing Assessments of Safety and Tolerability

7.1. Introduction

The safety profile of canagliflozin has been extensively studied in a comprehensive clinical development program involving diverse patient populations. Nonetheless, continued assessment of the safety profile of this agent is appropriate, to assure identification of rare events, not observed in the clinical program to date, and to continue to characterize the overall safety and tolerability profile of this agent with longer term treatment. Therefore the sponsor is committed to supplementing the current clinical database. Safety data collected from routine pharmacovigilance activities, from ongoing and future clinical trials conducted by the sponsor, and from a pharmacoepidemiology study will be used to further characterize the safety profile of canagliflozin. In addition, the sponsor is committed to the ongoing evaluation and implementation of risk management strategies where needed to ensure that the benefits of treatment with canagliflozin will outweigh identified risks.

7.2. Collection of Safety Information from Ongoing and Future Studies

With regard to safety information from ongoing and future studies of canagliflozin, the largest and longest experience will emerge from CANVAS (Study DIA3008), the CV safety study. This currently includes approximately 3300 subjects continuing in the trial (estimated to be approximately 2200 on canagliflozin), and is expected to continue at least through 2015, providing a mean duration of follow-up of approximately 5 to 6 years for all subjects. This study, along with the additional ongoing Phase 3 clinical trials (including studies DIA3009 and DIA3010, both of 2 year durations), will expand the longer term experience with canagliflozin treatment. In particular, these studies will continue to assess CV risk (with events largely emerging from CANVAS), with ongoing adjudication of CV events (by a blinded to treatment, independent panel), so as to meet the US FDA guidance requirement (demonstrating that the upper bound of the 95% CI is <1.3 post-approval). Furthermore, these studies will provide additional experience for fracture events, and additional information on malignancies, including renal cancer incidence. Assuming the expected relative risk of 1.0, the upper bound, based upon predicted number of accumulated events for these malignancies, is shown in Table 48. Given the limitations of the ongoing studies in excluding risk of these rare events, the sponsor proposes to conduct a pharmacoepidemiology study to provide additional information.

Table 48: Projected Upper Bounds for 95% Confidence Interval of Relative Risk (RR) Excludable with High Probability

Event	Observed Incidence per 1000 Subject-Years Within Phase 3 Program	Total Number of Events Likely Reported at Completion of Ongoing Clinical Trials*	Upper Bound of RR Excludable with Probability of 0.8
Renal cell cancer	0.57	16	4.42
Bladder cancer	0.64	18	4.06
Breast cancer	3.02	36	2.69
Fracture	15.7	364	1.36

* Assuming total number of events will be double those observed to 15Nov2012 for renal, bladder and breast cancer and 01Jul-2012.

Note: RR upper bound excludable calculated in Episheet®, assuming observed incidence remains constant, true RR=1, subject-years distributed 2:1 for canagliflozin:non-canagliflozin as randomized, and subject-years as sample size equivalent to subject counts.

7.3. Proposed Pharmacoepidemiology Study

As noted, the sponsor is committed to conducting a pharmacoepidemiological study in adult patients with T2DM, as part of the canagliflozin post-approval surveillance activities. This will focus on the incidence of renal cell cancer, but will facilitate the collection of information on other endpoints. Although the preclinical toxicology studies have shown that the finding of RTTs in rats is not relevant for human risk (see Section 2) and no imbalance in renal cancers was seen in the clinical development program, this will be further evaluated using the proposed pharmacoepidemiology study. Such a study may also provide additional information on other malignancies, such as searching for occurrence of the rare tumors seen in the 2-year carcinogenicity study (LCTs and pheochromocytoma). Although the ongoing clinical trial database will provide substantive experience with regard to fracture risk, the pharmacoepidemiology study will provide additional information, including assessments in broader populations. The primary comparison of interest will be patients with T2DM taking canagliflozin as compared with patients with T2DM not taking canagliflozin. During study protocol development, the sponsor will seek input and feedback from the FDA and external collaborators to design a rigorous study that can address important safety questions. Details will be provided on sample size requirement and appropriate data source, outcome measures and validation, control of confounding and biases, as well as plans for analysis. The sponsor is seeking to identify databases that provide complete longitudinal follow-up, and are linked to data on tumor characteristics and subject's vital status. The sponsor recognizes the potential confounding bias due to differences in the use of diagnostic testing (eg, urinalysis) that may impact rates of renal cell cancer diagnosis, and will work to incorporate design features to reduce this bias.

8. BENEFIT-RISK ASSESSMENT

Canagliflozin is a new oral agent acting by a novel, insulin-independent mechanism of action to improve glycemic control in adults with T2DM who are inadequately controlled on their current treatment regimen. Canagliflozin acts by inhibiting SGLT2, a transporter protein in the proximal tubule of the kidney that reabsorbs glucose filtered by the glomerulus. Results of an extensive

Phase 3 clinical development program show that canagliflozin has the potential to be a valuable addition to currently available therapeutic options: once-daily administration of canagliflozin 100 mg and 300 mg provided substantial improvements in overall glycemic control as reflected by HbA_{1c} reductions—reducing both fasting and post-meal glucose values—and by getting a large proportion of patients to glycemic goals across studies. When used as monotherapy or in combinations with agents not associated with hypoglycemia, canagliflozin treatment was associated with a low incidence of hypoglycemia. In addition to the improvements in glycemic control, decreases in body weight, and reductions in systolic and to a lesser extent diastolic BP were seen across clinical studies.

The improved glycemic control seen with canagliflozin was observed across the full continuum of patients with T2DM, from individuals early in their disease used as monotherapy to those with long-standing disease used as add-on to complicated insulin regimens; further, consistent glycemic improvements were seen across patient subgroups defined by demographic or anthropometric characteristics, with marked improvements in glycemic control in patients with higher baseline HbA_{1c} (even getting some subjects with baseline HbA_{1c} values >10%, in the substudy of the monotherapy trial, to glycemic goal of <7%). The mechanism of action of canagliflozin, increasing UGE and directly lowering glucose concentrations, is entirely distinct from the mechanisms by which other classes of AHAs lower glucose, and is independent of insulin. These observations show that canagliflozin can provide clinical value when added to a broad range of AHAs, and across the broad spectrum of the disease.

Glycemic efficacy was demonstrated in subjects with reduced eGFR values (NKF Stage 3 renal disease: eGFR ≥30 to <60 mL/min/1.73 m^2), albeit with a lesser extent of glucose-lowering than seen in subjects with normal renal function or only mild renal impairment. Nonetheless, canagliflozin got more of these subjects to glycemic goal (HbA_{1c} <7%), thereby providing clinical value. The treatment options for patients with reduced eGFR (NKF Stage 3) are limited: metformin is contraindicated as renal function decreases, and PPARγ agents must be used cautiously; insulin and sulphonylurea agents may lead to weight gain, edema, or hypoglycemia—all problematic in these more vulnerable patients. With a number of classes of AHAs either with limitations or contraindications, canagliflozin can provide another option for physicians managing such challenging patients. Canagliflozin also provided improvements in BP in these patients; since many patients with renal impairment are not achieving blood pressure goals, the improvements in BP with canagliflozin are also clinically useful.

Both doses of canagliflozin provided clinically important glycemic improvements, with the 300 mg dose providing greater reductions in glycemic endpoints (including HbA_{1c}, FPG, post-meal glucose), in body weight, and greater reductions in BP. Since the relationship between improvements in glycemic control and reduction in the risk of microvascular complications of diabetes is continuous (until normoglycemia is reached) (UKPDS 2000, DCCT 1993), the additional glucose-lowering efficacy of the canagliflozin 300 mg dose should translate to clinical benefit. A dose-related higher incidence of adverse events related to reduced intravascular volume (such as postural dizziness) that were non-serious, generally of mild to moderate intensity, and infrequently led to discontinuation was seen with canagliflozin; analyses identified

risk factors for these adverse events predicting greater dose-related increases in occurrence (age ≥75 years, eGFR <60 mL/min/1.73 m^2, use of loop diuretics) that can be used to guide the decision to start with the 100 mg or 300 mg dose. Since many patients still present with poorer glycemic control, with higher HbA_{1c} values, the greater glucose-lowering response with canagliflozin 300 mg should prove valuable, helping more patients achieve glycemic goals.

Several Phase 3 studies examined fasting and post-meal beta-cell function and demonstrated improvements with canagliflozin; in an active-comparator controlled study, these improvements were similar to those provided by sitagliptin, an agent that has a beta-cell directed mechanism of action. As discussed above, the primary mechanism by which canagliflozin lowers glucose is by moving glucose out of the system through the kidney, directly lowering glucose concentrations; the improvements seen in beta-cell function could simply reflect reversal of glucotoxicity (the negative effect of elevated glucose on insulin secretion), but the impact of weight loss, with attendant improvements in insulin sensitivity reducing beta-cell demand, or downstream benefits of the metabolic shifts attendant to removing glucose through UGE, may also play a role. Progressive deterioration in beta-cell function underlies the progressive deterioration in glycemic control in patients with T2DM (Alan 2011, UKPDS 2000). These indirect mechanisms of improvement in beta-cell function with canagliflozin may help to explain the sustained responses in FPG and HbA_{1c} to this agent seen in the two 52-week Phase 3 active-controlled trials—relative to the deterioration in glycemic response seen with the comparators (sitagliptin and glimepiride) acting directly on the beta cell to increase insulin secretion—agents from two of the most commonly used AHA classes. Given the progressive deterioration of beta cell function seen in T2DM, an antihyperglycemic agent with sustained HbA_{1c} lowering could lengthen the time to addition of another antihyperglycemic agent.

The weight loss provided by canagliflozin may also be clinically useful. Adherence to medications is a key problem, interfering with goal attainment for all chronic diseases, including diabetes (Delamater 2006). For patients with T2DM, who are often overweight or obese, and who struggle with their weight, an AHA that does not increase body weight, and even provides weight loss, is highly desirable (Blonde 2009) and may enhance compliance (just as weight gain associated with several other AHAs may reduce adherence) (Nau 2012). In addition, since obesity contributes to the pathogenesis of T2DM by increasing insulin resistance, reductions in body weight are desirable, and considered an important part of the medical management of this disease.

Despite the availability of other classes of oral agents for the treatment of patients with T2DM, approximately half of all patients do not achieve or maintain glycemic goals (Lawrence 2006). There are many reasons for this consistent observation, but the limited effectiveness and lack of sustained HbA_{1c}-lowering response to many current oral AHAs treatments likely contributes. The substantial decreases in HbA_{1c} with canagliflozin that were more sustained then commonly used comparator AHAs, as discussed above, suggests that canagliflozin may reduce the need for additional therapies over time—and this was reflected in a low requirement for rescue glycemic therapy in the canagliflozin treatment groups across the Phase 3 program. When a patient has inadequate control on metformin, the physician's choices for oral agents to add to the patient's

regimen are limited: addition of a PPARγ agent (that can lead to weight gain, edema, and an increased fracture risk), or of an alpha-glucosidase inhibitor (that has limited efficacy, and substantial gastrointestinal intolerance), or of a sulphonylurea agent (that has poorer durability, weight gain, and the risk of hypoglycemia), or of a DPP-4 inhibitor (well tolerated, weight neutral). With canagliflozin, the physician would have an option to add an agent that provides substantial and sustained HbA_{1c}-lowering, a low risk of hypoglycemia, while avoiding weight gain (and providing weight loss). These advantages come with safety and tolerability issues that must be considered, as discussed below, but help to frame the substantial clinical value that canagliflozin may provide in the stepwise care of patients with T2DM.

Canagliflozin treatment led to a dose-related increase in LDL-C (with a mean increase of approximately 4.36 mg/dL and 8.15 mg/dL at the 100 mg and 300 mg doses, respectively). This increase in LDL-C was associated with lesser increases in other measures of Apo B-containing particles such as non-HDL-C, LDL-C particle number, or directly-measured Apo B. Since LDL-C is an established CV risk factor and accepted surrogate endpoint, this increase in LDL-C, if not properly managed, could reduce the potential overall benefit of canagliflozin treatment. The LDL-C-lowering response to statin therapy did not appear to be affected by canagliflozin treatment. The increase must be viewed in the context of improvement in BP, an established CV risk factor and accepted surrogate endpoint, and the proportionately smaller rises in non-HDL-C, Apo B, and LDL-C particle number also important CV risk factors related to LDL-C. Other improvements with canagliflozin, such as in HDL-C, TG, body weight, glycemic control reflect changes in measures not established as surrogate endpoints, and thus cannot be considered to counterbalance the potential clinical relevance of the rise in LDL-C. The pre-specified program-wide CV meta-analysis results showed that the HR for MACE-plus events (based upon a time to event analysis) was 0.91 (95% CI: 0.68 to 1.22), and was similar at both doses of canagliflozin. Although the CV meta-analysis results must be considered preliminary (with ongoing collection of events, and subsequent meta-analyses planned), there was no signal for an increase in the MACE-plus composite. Analyses applying a range of CV risk engines, which must be viewed with caution since none are validated as predictive, did not suggest any increase in CV risk with either dose of canagliflozin. Physicians using canagliflozin will need to be aware of the potential for increases in LDL-C, and implement appropriate, aggressive management of fasting lipids to assure that patients continue to achieve goal LDL-C levels.

A comprehensive evaluation of safety and tolerability has been performed for canagliflozin, including 12,795 subjects enrolled in Phase 1, 2 and 3 studies, nearly 4,500 subjects on canagliflozin with approximately a year or more exposure. The extensive Phase 3 clinical program included studies older subjects and in subjects with a high prevalence of comorbidities and diabetic complications, thus allowing the safety evaluation to be conducted in a more vulnerable population. These evaluations showed that canagliflozin was generally well tolerated, with no notable increase in serious adverse events and deaths. Most oral AHAs for the treatment of T2DM have specific safety or tolerability issues—including gastrointestinal adverse events (such as with metformin), edema, fractures, and weight gain (such as with PPARγ agonists) or hypoglycemia (such as with SU agents). Canagliflozin also has specific safety and tolerability issues that were well characterized in this development program, and can be described in

prescribing information (such as the genital mycotic infections, UTIs, osmotic diuresis-related adverse events, reduced intravascular volume-related adverse events, and increases in LDL-C) and well managed by the physician, and for some of these issues, by the patient. The low rate of discontinuation from clinical studies of canagliflozin, only slightly higher than seen in the control group, supports the conclusion that this agent was generally well tolerated.

Both the 100 mg and the 300 mg doses of canagliflozin provide substantial and sustained reductions in HbA_{1c}, with improvements in both fasting and post-meal glucose levels, with additional potentially valuable clinical benefits on blood pressure and body weight, with a well-defined safety and tolerability profile that supports the use in the proposed patient population. The proposed prescribing information for this agent will clearly describe the efficacy and safety profile and provides appropriate directions and advice. In summary, canagliflozin is a valuable new agent in the armamentarium for the treatment of patients with T2DM.

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ATTACHMENTS

Attachment 1:
Non-clinical Results

Table 1: Urinary Calcium, Hyperostosis, 1,25-Dihydroxyvitamin D, and Parathyroid Hormone in the GLP 6-Month Glucose/Galactose-Free Fructose Diet Intervention Rat Study (TOX10093)

Diet		Standard	Standard	Fructose	Fructose
Canagliflozin Dose (mg/kg/day)		0	100	0	100
Urinary Calcium	1 Month, 0-6h	0.196	**11.15x*** **	**0.23x*** **	1.00x
	3 Months, 0-6h	0.139	**13.84x*** **	**0.38x*** **	**1.89x*** **
	6 Months, 0-6h	0.216	**8.73x*** **	0.880x	**1.76x***
Hyperostosis, Sternum	1 Month	0/10	**8/10****	0/9	0/10
Hyperostosis, Stifle	1 Month	0/10	**9/10****	0/10	0/9
Hyperostosis, Sternum	3 Months	0/10	**8/10****	0/10	0/10
Hyperostosis, Stifle	3 Months	0/10	**9/10****	0/10	1/10
Hyperostosis, Sternum	6 Months	0/10	**8/10****	0/10	0/9
Hyperostosis, Stifle	6 Months	0/10	**9/10****	0/10	0/9
1,25-Dihydroxyvitamin D	1 Month	145.06	**0.18x*** **	**2.48x****	0.56x
(pmol/mL)	3 Months	76.20	**0.35x***	1.28x	**0.35x***
	6 Months	30.18	0.88x	1.16x	0.88x
Parathyroid Hormone	1 Month	404.95	**0.19x*** **	1.20x	0.73x
(pg/mL)	3 Months	339.38	**0.18x*** **	1.86x	0.95x
	6 Months	314.81	**0.13x*** **	**1.39x***	0.96x

x = multiple compared to the standard diet control
*p≤0.05, **p≤0.01, ***p≤0.001
Bolded values are statistically significant compared to the standard diet control

Table 2: Tumor Incidence and Systemic Exposure Multiples in the Rat Carcinogenicity Study (TOX8986)

	MALES				FEMALES			
Dose Group (mg/kg/day):	0	10	30	100	0	10	30	100
ADRENAL GLANDS								
N /group	*65*	*64*	*64*	*65*	*65*	*63*	*62*	*64*
Pheos benign	4	4	7	**26**	2	1	3	**7**
Pheos malignant	-	-	1	**2**	-	-	-	-
KIDNEYS								
Adenoma renal tubule	-	-	1[a]	**8**	-	-	-	**7**
Carcinoma renal tubule	-	-	1[a]	**5**[b]	-	-	-	**2**
TESTES								
Leydig cell (interstitial cell)	1	**8**	**20**	**24**				
Exposure Multiples (AUC_{SS})								
300 mg clinical dose		1.5x	4.5x *	12x		2.4x	7.2x*	21x
100 mg clinical dose		5.4x	17x*	45x		8.7x	27x*	79x

Bolded value indicates a treatment-related effect; * Safety margins for adrenal and kidney tumors ; [a] spontaneous amphophilic-vacuolar (AV) tumor; [b] one tumor from this group was a spontaneous AV tumor

Table 3: Cell Proliferation in the GLP 6-Month Glucose/Galactose-Free Fructose Diet Interventional Rat Study (TOX10093)

Diet		Standard	Standard	Fructose	Fructose
Canagliflozin Dose (mg/kg/day)		0	100	0	100
Kidney BrDU Labeling					
Cortex (epithelial cells)[a]	1 Month	64	1.08x	1.25x	0.94x
	3 Months	42	**2.02x**	1.40x	1.26x
	6 Months	25	**2.76x**	1.52x	1.76x
OSOM[a]	1 Month	96	**1.39x**	1.25x	1.15x
	3 Months	66	**2.21x**	1.41x	1.56x
	6 Months	54	**2.52x**	1.50x	1.83x
Total (cortex + OSOM)[b]	1 Month	160	1.26x	1.25x	1.06x
	3 Months	108	**2.14x**	1.41x	1.44x
	6 Months	79	**2.59x**	1.51x	1.81x
Adrenal Gland BrDU Labeling					
Adrenal Gland (medulla)[c]	1 Month	179	**1.79x**	0.97x	0.90x
	3 Months	70	**2.24x**	1.19x	1.51x
	6 Months	38	**2.26x**	0.84x	1.45x

Key: OSOM = outer stripe of the outer medulla; x = multiple compared to standard diet control
[a] the average positive cells/1000 basal cells
[b] the average positive cells/2000 basal cells in the combined areas of the kidney cortex and OSOM
[c] the average number of labeled cells per mm2 of medulla
Note: Bolded values are statistically significant ($p<0.05$) relative to standard diet controls.

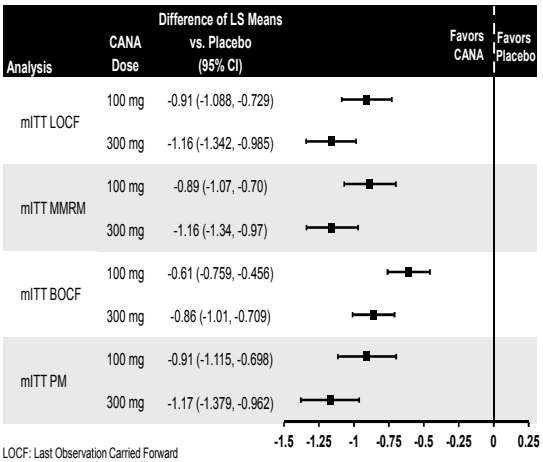
Table 4: KIM-1 Analysis of Kidney Cell Injury in the GLP 6-Month Glucose/Galactose-Free Fructose Diet Interventional Rat Study (TOX10093)

Diet		Standard	Standard	Fructose	Fructose
Canagliflozin Dose (mg/kg/day)		0	100	0	100
Kidney KIM-1 Labeling					
Cortex[a]	6 Months	0.02846	**13.93x**	2.60x	6.04x
OSOM[a]	6 Months	0.03063	**10.67x**	2.74x	4.18x
Total (cortex + OSOM)[b]	6 Months	0.05909	**12.24x**	2.67x	5.07x

Key: OSOM = outer stripe of the outer medulla; x = multiple compared to standard diet control
[a] The average positive epithelial cells/1000 basal cells
[b] The average positive epithelial cells/2000 basal cells in the combined areas of the kidney cortex and OSOM
Note: Bolded values are statistically significant ($p<0.05$) relative to the standard diet control.

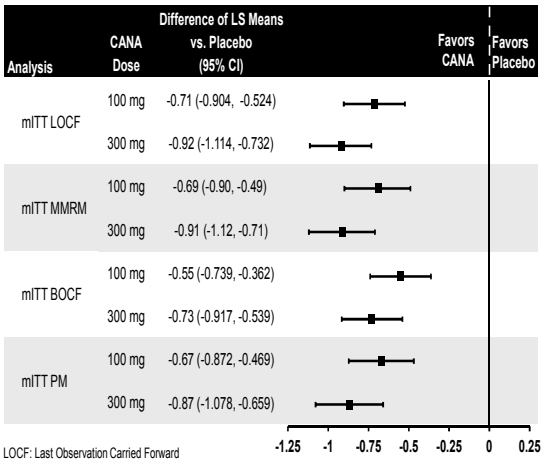
Attachment 2:
Summaries of Primary and Sensitivity Analyses for Phase 3 Studies

Summary of Primary and Sensitivity Analyses
Monotherapy Study (DIA3005)



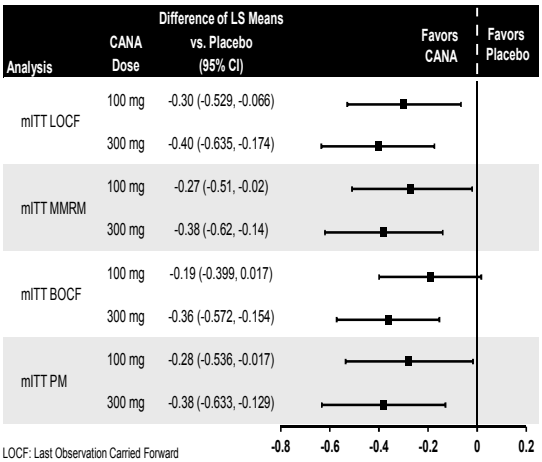
LOCF: Last Observation Carried Forward
MMRM: Mixed Model Repeated Measures
BOCF: Baseline Observation Carried Forward
PM: Pattern Mixture model

Summary of Primary and Sensitivity Analyses
Placebo-controlled Add-on to Metformin + SU Study (DIA3002)



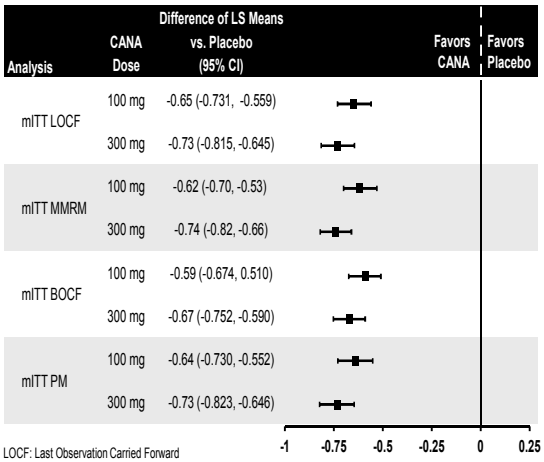
LOCF: Last Observation Carried Forward
MMRM: Mixed Model Repeated Measures
BOCF: Baseline Observation Carried Forward
PM: Pattern Mixture model

Summary of Primary and Sensitivity Analyses
Study in Subjects with T2DM and
Moderate Renal Impairment (DIA3004)



LOCF: Last Observation Carried Forward
MMRM: Mixed Model Repeated Measures
BOCF: Baseline Observation Carried Forward
PM: Pattern Mixture model

Summary of Primary and Sensitivity Analyses
Placebo-controlled Add-on to Insulin Substudy (DIA3008 Insulin)

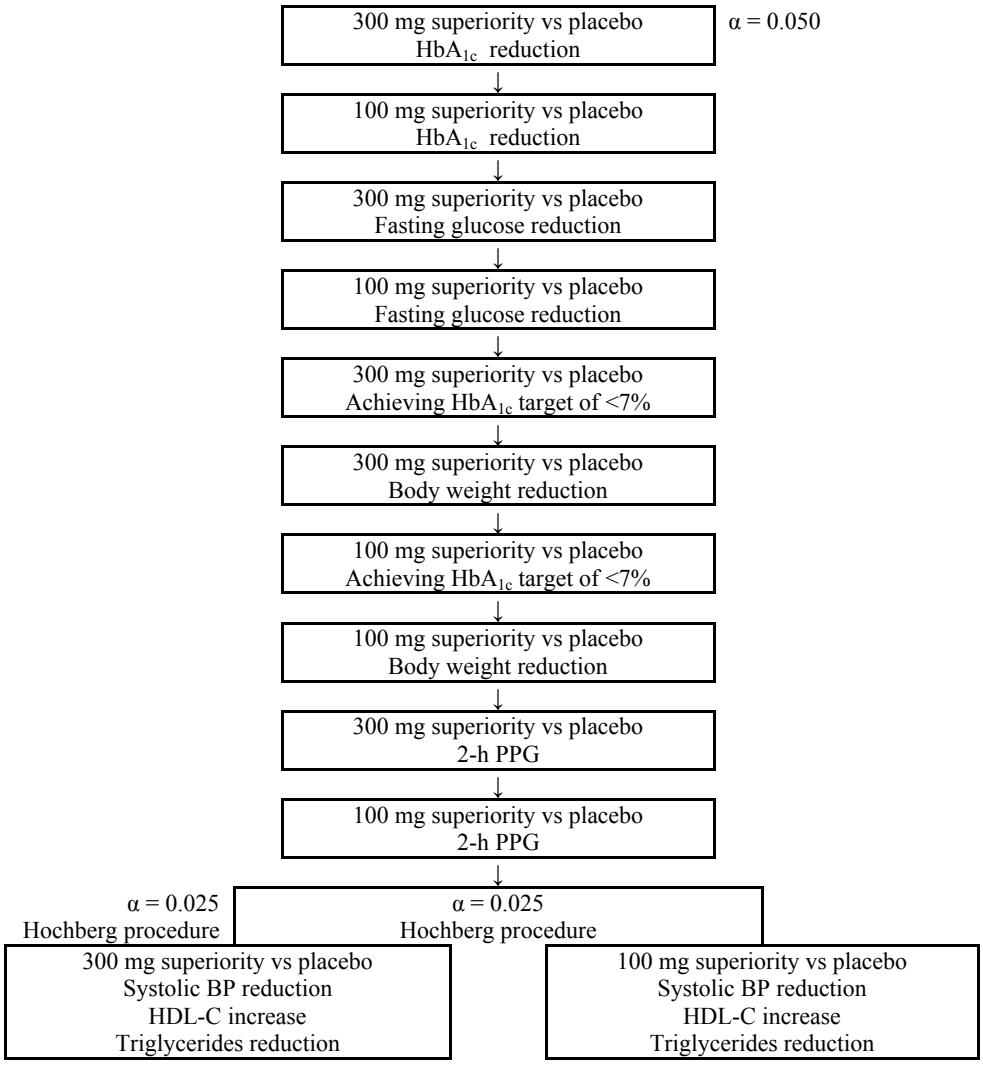


LOCF: Last Observation Carried Forward
MMRM: Mixed Model Repeated Measures
BOCF: Baseline Observation Carried Forward
PM: Pattern Mixture model

Attachment 3:
Multiplicity Adjustment for Studies DIA3005 and DIA3009

Study DIA3005

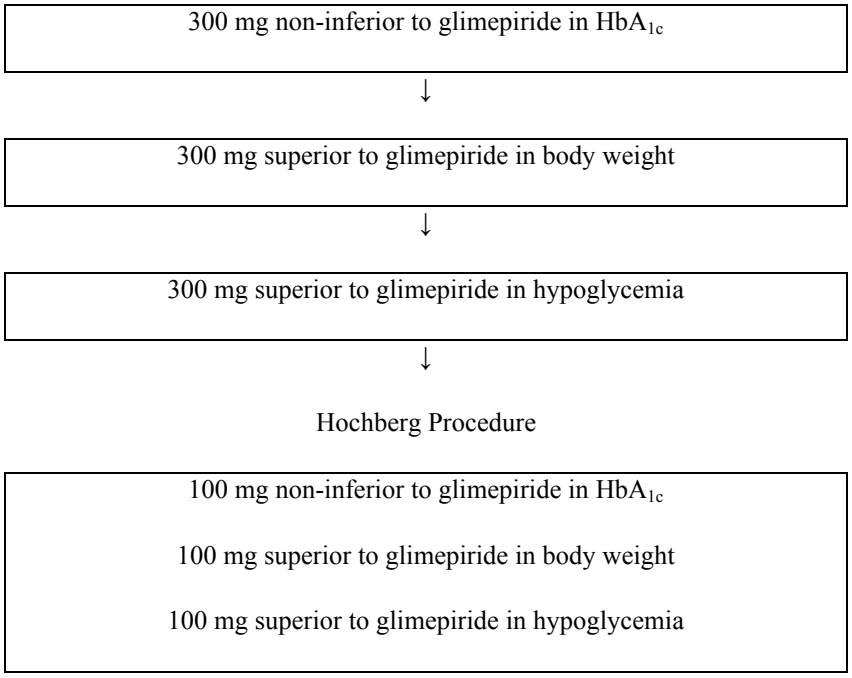
Hierarchy of Testing Hypotheses in the Main Study



Key: HbA_{1c}= hemoglobin A_{1c}; HDL-C=high-density lipoprotein cholesterol; PPG=postprandial plasma glucose

Study DIA3009

Hierarchy for Hypotheses Testing



Key: HbA_{1c}= hemoglobin A_{1c}

Attachment 4:
Subject Disposition to the Primary Endpoint– Phase 3 Study-by-Study Comparison

Study Type/ Study ID	Non-Cana	CANA 100 mg	CANA 300 mg
Monotherapy,			
DIA3005 - Main Study	N=194	N=196	N=197
Subjects randomized	194 (100.0)	196 (100.0)	197 (100.0)
Subjects in the mITT Analysis Set	192 (99.0)	195 (99.5)	197 (100.0)
Discontinued Prior to Primary Endpoint	32 (16.5)	23 (11.7)	22 (11.2)
Received Rescue Therapy Prior to Primary Endpoint	44 (22.7)	5 (2.6)	4 (2.0)
Completer Analysis Set[a]	121 (62.4)	168 (85.7)	171 (86.8)
DIA3005 – High Glycemic substudy		N=47	N=44
Subjects randomized		47 (100.0)	44 (100.0)
Subjects in mITT Analysis Set		47 (100.0)	44 (100.0)
Discontinued Prior to Primary Endpoint		7 (14.9)	4 (9.1)
Received Rescue Therapy		3 (6.4)	2 (4.5)
Dual therapy			
DIA3006 –Add-on to metformin	N=549	N=368	N=367
Subjects randomized	549 (100.0)	368 (100.0)	367 (100.0)
Subjects in mITT Analysis Set	549 (100.0)	368 (100.0)	367 (100.0)
Discontinued Prior to Primary Endpoint	75 (13.7)	46 (12.5)	44 (12.0)
Received Rescue Therapy Prior to Primary Endpoint	50 (9.1)	6 (1.6)	1 (0.3)
Completer Analysis Set[a]	429 (78.1)	317 (86.1)	322 (87.7)
DIA 3009 – Add-on to metformin	N=484	N=483	N=485
Subjects randomized	484 (100.0)	483 (100.0)	485 (100.0)
Subjects in mITT Analysis Set	482 (99.6)	483 (100.0)	485 (100.0)
Discontinued Prior to Primary Endpoint	96 (19.8)	88 (18.2)	105 (21.6)
Received Rescue Therapy Prior to Primary Endpoint	51 (10.5)	32 (6.6)	24 (4.9)
Completer Analysis Set[b]	337 (69.6)	365 (75.6)	357 (73.6)
DIA3008 substudy – Add-on to SU	N=45	N=42	N=40
Subjects randomized	45 (100.0)	42 (100.0)	40 (100.0)
Subjects in mITT Analysis Set	45 (100.0)	42 (100.0)	40 (100.0)
Discontinued Prior to Primary Endpoint	3 (6.7)	3 (7.1)	2 (5.0)
Received Rescue Therapy Prior to Primary Endpoint	8 (17.8)	2 (4.8)	0
Completer Analysis Set[c]	34 (75.6)	37 (88.1)	38 (95.0)
Triple therapy			
DIA3002 – Add-on to metformin and SU	N=156	N=157	N=156
Subjects randomized	156 (100.0)	157 (100.0)	156 (100.0)
Subjects in mITT Analysis Set	156 (100.0)	157 (100.0)	156 (100.0)
Discontinued Prior to Primary Endpoint	33 (21.2)	28 (17.8)	27 (17.3)
Received Rescue Therapy Prior to Primary Endpoint	20 (12.8)	2 (1.3)	3 (1.9)
Completer Analysis Set[a]	107 (68.6)	127 (80.9)	126 (80.8)
DIA3012 – Add-on to metformin and PIO	N=115	N=115	N=114
Subjects randomized	115 (100.0)	115 (100.0)	114 (100.0)
Subjects in mITT Analysis Set	115 (100.0)	113 (98.3)	114 (100.0)
Discontinued Prior to Primary Endpoint	24 (20.9)	9 (7.8)	13 (11.4)
Received Rescue Therapy Prior to Primary Endpoint	14 (12.2)	1 (0.9)	0
Completer Analysis Set[a]	79 (68.7)	103 (89.6)	101 (88.6)
DIA3015 – Add-on to metformin and SU	N=378		N=378
Subjects randomized	378 (100.0)		378 (100.0)
Subjects in mITT Analysis Set	378 (100.0)		377 (99.7)
Discontinued Prior to Primary Endpoint	168 (44.4)		123 (32.5)
Completer Analysis Set	210 (55.6)		254 (67.2)
Add-on to insulin			
DIA3008 substudy	N=565	N=566	N=587
Subjects randomized	565 (100.0)	566 (100.0)	587 (100.0)

Study Type/ Study ID	Non-Cana	CANA 100 mg	CANA 300 mg
Subjects in mITT Analysis Set	565 (100.0)	566 (100.0)	587 (100.0)
Discontinued Prior to Primary Endpoint	48 (8.5)	32 (5.7)	44 (7.5)
Received Rescue Therapy Prior to Primary Endpoint	49 (8.7)	23 (4.1)	18 (3.1)
Completer Analysis Set[c]	465 (82.3)	506 (89.4)	520 (88.6)
Special populations			
DIA3004 - renal impairment	N=91	N=90	N=91
Subjects randomized	91 (100.0)	90 (100.0)	91 (100.0)
Subjects in mITT Analysis Set	90 (98.9)	90 (100.0)	89 (97.8)
Discontinued Prior to Primary Endpoint	13 (14.3)	15 (16.7)	7 (7.7)
Received Rescue Therapy Prior to Primary Endpoint	13 (14.3)	4 (4.4)	3 (3.3)
Completer Analysis Set[a]	65 (71.4)	72 (80.0)	79 (86.8)
DIA3010 - older adults	N=239	N=241	N=236
Subjects randomized	239 (100.0)	241 (100.0)	236 (100.0)
Subjects in mITT Analysis Set	237 (99.2)	241 (100.0)	236 (100.0)
Discontinued Prior to Primary Endpoint	40 (16.7)	15 (6.2)	27 (11.4)
Received Rescue Therapy Prior to Primary Endpoint	26 (10.9)	5 (2.1)	1 (0.4)
Completer Analysis Set[a]	172 (72.0)	221 (91.7)	208 (88.1)
DIA3008 – Main study	N=1442	N=1445	N=1443
Subjects randomized	1442 (100)	1445 (100)	1443 (100)
Subjects discontinued	247 (17.1)	188 (13.0)	218 (15.1)
Received Rescue Therapy Prior to Week 18 visit	111 (7.7)	52 (3.6)	30 (2.1)
Continuing in study	1195 (82.9)	1257 (87.0)	1225 (84.9)

[a] Includes mITT subjects who completed the week 26 visit and **had not initiated rescue medication.**
[b] Includes mITT subjects who completed week 52 visit and **have not initiated rescue medication.**
[c] Includes mITT subjects who completed the substudy (ie, defined as having a Week 18 visit and not discontinuing double-blind medication prior to Day 119) and **have not initiated rescue medication.**
Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: tsub03dm_core_rds.rtf generated by rds.sas, 21MAR2012 15:41; tsub03ds_rds.rtf generated by rds.sas, 06DEC2011 10:18; tsub03d_core_rds.rtf generated by rds.sas, 06MAR2012 13:44; tsub03d_rds.rtf generated by rds.sas, 17APR2012 19:12; tsub03d_rds.rtf generated by rds.sas, 05MAR2012 11:33; tsub03d_core_p1_rds.rtf generated by rds.sas, 05MAR2012 16:44; tsub03c_core_rds.rtf generated by rds.sas, 05MAR2012 10:26; tsub03d_core_rds.rtf generated by rds.sas, 05MAR2012 11:51; tsub03d_rds.rtf generated by rds.sas, 23APR2012 10:51; tsub03d_core_p2_rds.rtf generated by rds.sas, 05MAR2012 12:38; tsub03dm_core_rds.rtf generated by rds.sas, 20MAR2012 22:56; tsub03dm_core_rds.rtf generated by rds.sas, 17APR2012 14:01

Attachment 5:
Demographic and Baseline Anthropometric and Diabetes Characteristics – Study-by-Study Comparison (Phase 3 Studies)

Characteristic	Monotherapy	Dual Therapy			Triple Therapy			Add-on to Insulin	Special Populations	
	DIA3005	DIA3006 Add-on to Met	DIA3009 Add-on to Met	DIA3008 SU Subst.	DIA3002 Add-on to Met + SU	DIA3015 Add-on to Met + SU	DIA3012 Add-on to Met + PIO	DIA3008 Subst.[a]	DIA3004 Renal Impairment	DIA3010 Older Adults
Age (years)										
N	584	1284	1450	127	469	755	342	1718	269	714
Mean (SD)	55.4 (10.61)	55.4 (9.42)	56.2 (9.22)	64.8 (7.65)	56.7 (9.30)	56.7 (9.46)	57.4 (10.03)	62.8 (7.65)	68.5 (8.28)	63.6 (6.24)
Median	56.0	56.0	57.0	65.0	58.0	57.0	57.0	63.0	69.0	63.0
Range	(24;79)	(21;79)	(22;80)	(44;82)	(27;79)	(21;91)	(27;78)	(32;85)	(39;96)	(55;80)
Category, n (%)										
<35	21 (3.6)	19 (1.5)	20 (1.4)	0	6 (1.3)	10 (1.3)	2 (0.6)	1 (0.1)	0	0
35 – <65	445 (76.2)	1059 (82.5)	1187 (81.9)	58 (45.7)	379 (80.8)	601 (79.6)	247 (72.2)	1017(59.2)	83 (30.9)	441 (61.8)
≥65	118 (20.2)	206 (16.0)	243 (16.8)	69 (54.3)	84 (17.9)	144 (19.1)	93 (27.2)	700 (40.7)	186 (69.1)	273 (38.2)
Sex, n (%)										
N	584	1284	1450	127	469	755	342	1718	269	714
Male	258 (44.2)	605 (47.1)	756 (52.1)	72 (56.7)	239 (51.0)	422 (55.9)	216 (63.2)	1143 (66.5)	163 (60.6)	396 (55.5)
Female	326 (55.8)	679 (52.9)	694 (47.9)	55 (43.3)	230 (49.0)	333 (44.1)	126 (36.8)	575 (33.5)	106 (39.4)	318 (44.5)
Race, n (%)										
N	584	1284	1450	127	469	755	342	1718	269	714
White	395 (67.6)	901 (70.2)	978 (67.4)	95 (74.8)	387 (82.5)	485 (64.2)	252 (73.7)	1342 (78.1)	215 (79.9)	552 (77.3)
Black, African-American	41 (7.0)	45 (3.5)	61 (4.2)	1 (0.8)	26 (5.5)	88 (11.7)	20 (5.8)	45 (2.6)	5 (1.9)	57 (8.0)
Asian	85 (14.6)	182 (14.2)	284 (19.6)	29 (22.8)	4 (0.9)	132 (17.5)	55 (16.1)	230 (13.4)	27 (10.0)	61 (8.5)
Other	63 (10.8)	156 (12.1)	127 (8.8)	2 (1.6)	52 (11.1)	50 (6.6)	15 (4.4)	101 (5.9)	22 (8.2)	44 (6.2)
Ethnicity, n (%)										
N	584	1284	1450	127	469	755	342	1718	269	714
Hispanic or Latino	180 (30.8)	373 (29.0)	242 (16.7)	11 (8.7)	109 (23.2)	159 (21.1)	54 (15.8)	121 (7.0)	21 (7.8)	104 (14.6)
Not Hispanic or Latino	402 (68.8)	908 (70.7)	1202 (82.9)	116 (91.3)	359 (76.5)	594 (78.7)	283 (82.7)	1591 (92.6)	240 (89.2)	607 (85.0)
Unknown/Not reported	2 (0.3)	3 (0.3)	6 (0.4)	0	1 (0.2)	2 (0.2)	5 (1.5)	6 (0.4)	8 (3.0)	3 (0.4)
Baseline BMI (kg/m^2)										
N	584	1283	1450	127	469	755	342	1715	269	714
Mean (SD)	31.6 (6.24)	31.8 (6.24)	31.0 (5.41)	29.9 (5.79)	33.0 (6.48)	31.6 (6.91)	32.6 (6.76)	33.8 (6.29)	33.0 (6.15)	31.6 (4.57)
Category, n (%)										
<30	266 (45.6)	565 (44.0)	673 (46.4)	72 (56.7)	159 (33.9)	355 (47.0)	133 (38.9)	491 (28.6)	87 (32.3)	270 (37.8)
≥30	318 (54.4)	718 (55.9)	777 (53.6)	55 (43.3)	310 (66.1)	400 (53.0)	209 (61.1)	1224 (71.2)	182 (67.7)	444 (62.2)
Baseline										

Characteristic	Monotherapy	Dual Therapy			Triple Therapy			Add-on to Insulin	Special Populations	
	DIA3005	DIA3006 Add-on to Met	DIA3009 Add-on to Met	DIA3008 SU Subst.	DIA3002 Add-on to Met + SU	DIA3015 Add-on to Met + SU	DIA3012 Add-on to Met + PIO	DIA3008 Subst.[a]	DIA3004 Renal Impairment	DIA3010 Older Adults
HbA_{1c} (%)										
N	584	1283	1450	127	469	755	342	1716	269	714
Mean (SD)	8.0 (0.97)	7.9 (0.90)	7.8 (0.79)	8.4 (1.00)	8.1 (0.92)	8.1 (0.91)	7.9 (0.96)	8.3 (0.90)	8.0 (0.87)	7.7 (0.78)
Category, n (%)										
<7.0%	68 (11.6)	161 (12.5)	195 (13.4)	3 (2.4)	33 (7.0)	64 (8.5)	43 (12.6)	59 (3.4)	29 (10.8)	108 (15.1)
7 - <8%	242 (41.4)	536 (41.7)	683 (47.1)	53 (41.7)	193 (41.2)	295 (39.1)	148 (43.3)	629 (36.6)	110 (40.9)	350 (49.0)
8 - <9%	177 (30.3)	402 (31.3)	441 (30.4)	33 (26.0)	152 (32.4)	247 (32.7)	91 (26.6)	642 (37.4)	94 (34.9)	202 (28.3)
9 - ≤10%	80 (13.7)	161 (12.5)	125 (8.6)	28 (22.0)	78 (16.6)	133 (17.6)	52 (15.2)	318 (18.5)	36 (13.4)[b]	53 (7.4)
>10%	17 (2.9)	23 (1.8)	6 (0.4)	10 (7.9)	13 (2.8)	16 (2.1)	8 (2.3)	68 (4.0)		1 (0.1)
Duration of diabetes (years)										
N	584	1284	1450	127	469	755	342	1718	269	714
Median	3.0	5.7	5.0	9.0	8.6	8.0	9.7	15.0	15.0	10.0
BL eGFR-(mL/min/1.73 m^2)										
N	584	1284	1449	125	469	755	342	1716	269	714
Mean (SD)	87.1 (20.28)	88.6 (18.47)	90.2 (18.74)	69.3 (18.55)	89.4 (19.65)	87.5 (19.14)	86.4 (18.59)	74.9 (19.02)	39.4 (6.88)	77.5 (16.57)
Median	85.0	87.0	88.2	69.0	88.0	86.0	84.0	74.0	39.0	76.0
Range	(38,227)	(44,169)	(33,181)	(32,116)	(26,163)	(50.0;164.0)	(48,144)	(27,159)	(24,61)	(37,153)
Category, n (%)										
<60	32 (5.5)	40 (3.1)	38 (2.6)	44 (35.2)	15 (3.2)	41 (5.4)	25 (7.3)	348 (20.3)	268 (99.6)	94 (13.2)
60 - <90	324 (55.5)	665 (51.8)	715 (49.3)	65 (51.2)	235 (50.1)	382 (50.6)	184 (53.8)	1014 (59.0)	1 (0.4)	456 (63.9)
≥90	228 (39.0)	579 (45.1)	696 (48.0)	16 (12.6)	219 (46.7)	332 (44.0)	133 (38.9)	354 (20.6)		164 (23.0)
Microvascular complication										
N	584	1284	1450	127	469	755	342	1718	269	714
n (%)	40 (6.8)	286 (22.3)	269 (18,6)	55 (43.3)	124 (26.4)	251 (33.2)	66 (19.3)	1026 (59.7)	216 (80.3)	212 (29.7)

[a] Data for DIA3008 Insulin substudy is presented for subjects receiving insulin dose ≥30 IU/day.
[b] For DIA3004, this baseline HbA_{1c} category was 9 to ≤10.5%.
Note: Percentages calculated with the number of subjects in each group as denominator.
Note: mITT analysis set
Cross-reference: ISE Table 20, Table 21 and Table 22

Attachment 6:
Baseline Demographic and Anthropometric Characteristics in Placebo-controlled Studies Dataset

	-- Placebo -- (N=646)	Cana 100 mg (N=833)	Cana 300 mg (N=834)	-- All Cana - (N=1667)	--- Total --- (N=2313)
Sex, n (%)					
N	646	833	834	1667	2313
Male	334 (51.7)	408 (49.0)	404 (48.4)	812 (48.7)	1146 (49.5)
Female	312 (48.3)	425 (51.0)	430 (51.6)	855 (51.3)	1167 (50.5)
Age (Years)					
N	646	833	834	1667	2313
Category, n (%)					
<35	14 (2.2)	17 (2.0)	12 (1.4)	29 (1.7)	43 (1.9)
35 -<65	495 (76.6)	657 (78.9)	673 (80.7)	1330 (79.8)	1825 (78.9)
65 -<75	122 (18.9)	138 (16.6)	132 (15.8)	270 (16.2)	392 (16.9)
≥75	15 (2.3)	21 (2.5)	17 (2.0)	38 (2.3)	53 (2.3)
≥85	0	0	0	0	0
Mean (SD)	56.3 (9.80)	55.9 (10.10)	55.7 (9.53)	55.8 (9.81)	56.0 (9.81)
Median	57.0	56.0	56.0	56.0	57.0
Range	(24;79)	(26;79)	(21;79)	(21;79)	(21;79)
Race, n (%)					
N	646	833	834	1667	2313
White	470 (72.8)	591 (70.9)	610 (73.1)	1201 (72.0)	1671 (72.2)
Black or African American	28 (4.3)	43 (5.2)	48 (5.8)	91 (5.5)	119 (5.1)
Asian	82 (12.7)	103 (12.4)	100 (12.0)	203 (12.2)	285 (12.3)
American Indian or Alaska Native	7 (1.1)	9 (1.1)	9 (1.1)	18 (1.1)	25 (1.1)
Native Hawaiian or Other Pacific Islander	2 (0.3)	0	1 (0.1)	1 (0.1)	3 (0.1)
Multiple	1 (0.2)	0	4 (0.5)	4 (0.2)	5 (0.2)
Other	52 (8.0)	84 (10.1)	61 (7.3)	145 (8.7)	197 (8.5)
Unknown	0	1 (0.1)	0	1 (0.1)	1 (<0.1)
Not Reported	4 (0.6)	2 (0.2)	1 (0.1)	3 (0.2)	7 (0.3)
Ethnicity, n (%)					
N	646	833	834	1667	2313
Hispanic or Latino	175 (27.1)	213 (25.6)	221 (26.5)	434 (26.0)	609 (26.3)
Not Hispanic or Latino	471 (72.9)	615 (73.8)	609 (73.0)	1224 (73.4)	1695 (73.3)
Not Reported	0	2 (0.2)	2 (0.2)	4 (0.2)	4 (0.2)
Unknown	0	3 (0.4)	2 (0.2)	5 (0.3)	5 (0.2)
Baseline BMI (kg/m²)					
N	646	833	833	1666	2312
Category, n (%)					
<30	275 (42.6)	336 (40.3)	353 (42.3)	689 (41.3)	964 (41.7)
≥30	371 (57.4)	497 (59.7)	480 (57.6)	977 (58.6)	1348 (58.3)
Mean (SD)	31.9 (6.36)	32.3 (6.41)	32.0 (6.48)	32.1 (6.44)	32.1 (6.42)
Median	31.0	31.5	31.1	31.3	31.2
Range	(18;69)	(19;61)	(18;73)	(18;73)	(18;73)
Region, n (%)					
N	646	833	834	1667	2313
North America	303 (46.9)	381 (45.7)	369 (44.2)	750 (45.0)	1053 (45.5)
Central/South America	61 (9.4)	90 (10.8)	88 (10.6)	178 (10.7)	239 (10.3)
Europe	160 (24.8)	176 (21.1)	185 (22.2)	361 (21.7)	521 (22.5)
Rest of the World	122 (18.9)	186 (22.3)	192 (23.0)	378 (22.7)	500 (21.6)

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: tsub02_01_rsl.rtf generated by rsl.sas, 18APR2012 16:21

Attachment 7:
Duration of Exposure to Study Drug in Placebo-controlled Studies Dataset

	----- Placebo ----- (N=646)	--- Cana 100 mg --- (N=833)	--- Cana 300 mg --- (N=834)	----- All Cana ---- (N=1667)
Total duration of exposure (weeks)				
N	646	833	834	1667
Category, n (%)				
<2 weeks	7 (1.1)	10 (1.2)	9 (1.1)	19 (1.1)
2-<6 weeks	18 (2.8)	18 (2.2)	16 (1.9)	34 (2.0)
6-<12 weeks	16 (2.5)	35 (4.2)	30 (3.6)	65 (3.9)
12-<18 weeks	36 (5.6)	21 (2.5)	27 (3.2)	48 (2.9)
18-<24 weeks	32 (5.0)	21 (2.5)	19 (2.3)	40 (2.4)
≥24 weeks	537 (83.1)	728 (87.4)	733 (87.9)	1461 (87.6)
Mean (SD)	23.77 (5.93)	24.22 (5.70)	24.30 (5.53)	24.26 (5.61)
Median	26.00	26.14	26.14	26.14
Range	(0.1;28.6)	(0.1;30.0)	(0.1;31.1)	(0.1;31.1)
Total Exposure (subject years)	294.3	386.7	388.3	775.0

Note: Total duration = Treatment duration = last dose date - first dose date + 1(in days).
Cross-reference: ISS Table 17, tsub04r_01_rex.rtf generated by rex.sas, 18APR2012 16:47

Attachment 8:
Baseline Demographic and Anthropometric Characteristics in Broad Dataset
(through 01 July 2012)

	All Non-CANA (N=3262)	CANA 100 mg (N=3092)	CANA 300 mg (N=3085)	All CANA (N=6177)	Total (N=9439)
Sex, n (%)					
N	3262	3092	3085	6177	9439
Male	1924 (59.0)	1803 (58.3)	1766 (57.2)	3569 (57.8)	5493 (58.2)
Female	1338 (41.0)	1289 (41.7)	1319 (42.8)	2608 (42.2)	3946 (41.8)
Age (Years)					
N	3262	3092	3085	6177	9439
Category, n (%)					
<35	26 (0.8)	26 (0.8)	19 (0.6)	45 (0.7)	71 (0.8)
35 -<65	2259 (69.3)	2084 (67.4)	2095 (67.9)	4179 (67.7)	6438 (68.2)
65 -<75	822 (25.2)	819 (26.5)	799 (25.9)	1618 (26.2)	2440 (25.9)
≥75	155 (4.8)	163 (5.3)	172 (5.6)	335 (5.4)	490 (5.2)
≥85	5 (0.2)	1 (<0.1)	6 (0.2)	7 (0.1)	12 (0.1)
Mean (SD)	59.7 (9.24)	60.0 (9.45)	60.0 (9.35)	60.0 (9.40)	59.9 (9.35)
Median	60.0	60.0	61.0	60.0	60.0
Range	(24;96)	(22;85)	(21;90)	(21;90)	(21;96)
Race, n (%)					
N	3262	3092	3085	6177	9439
White	2382 (73.0)	2239 (72.4)	2236 (72.5)	4475 (72.4)	6857 (72.6)
Black or African American	118 (3.6)	115 (3.7)	126 (4.1)	241 (3.9)	359 (3.8)
Asian	506 (15.5)	496 (16.0)	491 (15.9)	987 (16.0)	1493 (15.8)
American Indian or Alaska Native	20 (0.6)	15 (0.5)	12 (0.4)	27 (0.4)	47 (0.5)
Native Hawaiian or Other Pacific Islander	5 (0.2)	4 (0.1)	6 (0.2)	10 (0.2)	15 (0.2)
Multiple	23 (0.7)	15 (0.5)	28 (0.9)	43 (0.7)	66 (0.7)
Other	202 (6.2)	204 (6.6)	183 (5.9)	387 (6.3)	589 (6.2)
Unknown	2 (0.1)	2 (0.1)	1 (<0.1)	3 (<0.1)	5 (0.1)
Not Reported	4 (0.1)	2 (0.1)	2 (0.1)	4 (0.1)	8 (0.1)
Ethnicity, n (%)					
N	3262	3092	3085	6177	9439
Hispanic or Latino	543 (16.6)	485 (15.7)	470 (15.2)	955 (15.5)	1498 (15.9)
Not Hispanic or Latino	2705 (82.9)	2593 (83.9)	2606 (84.5)	5199 (84.2)	7904 (83.7)
Not Reported	8 (0.2)	5 (0.2)	4 (0.1)	9 (0.1)	17 (0.2)
Unknown	6 (0.2)	9 (0.3)	5 (0.2)	14 (0.2)	20 (0.2)
Baseline BMI (kg/m²)					
N	3259	3090	3081	6171	9430
Category, n (%)					
<30	1363 (41.8)	1256 (40.6)	1272 (41.2)	2528 (40.9)	3891 (41.2)
≥30	1896 (58.1)	1834 (59.3)	1809 (58.6)	3643 (59.0)	5539 (58.7)
Mean (SD)	31.9 (6.08)	31.9 (6.03)	31.9 (6.05)	31.9 (6.04)	31.9 (6.06)
Median	31.1	31.2	31.2	31.2	31.2
Range	(17;69)	(18;71)	(18;73)	(18;73)	(17;73)
Region, n (%)					
N	3262	3092	3085	6177	9439
North America	1165 (35.7)	1123 (36.3)	1084 (35.1)	2207 (35.7)	3372 (35.7)
Central/South America	234 (7.2)	186 (6.0)	197 (6.4)	383 (6.2)	617 (6.5)
Europe	865 (26.5)	862 (27.9)	846 (27.4)	1708 (27.7)	2573 (27.3)
Rest of the World	998 (30.6)	921 (29.8)	958 (31.1)	1879 (30.4)	2877 (30.5)

Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: tsub02_03_rsl.rtf generated by rsl.sas, 18APR2012 17:23

Attachment 9:
Duration of Exposure to Study Drug in Broad Dataset (through 01 July 2012)

	--- All Non-CANA -- (N=3262)	-- CANA 100 mg -- (N=3092)	-- CANA 300 mg --- (N=3085)	----- All CANA ---- (N=6177)
Total duration of exposure (weeks)				
N	3262	3092	3085	6177
Category, n (%)				
<2 weeks	27 (0.8)	29 (0.9)	32 (1.0)	61 (1.0)
2-<6 weeks	76 (2.3)	52 (1.7)	85 (2.8)	137 (2.2)
6-<12 weeks	100 (3.1)	85 (2.7)	85 (2.8)	170 (2.8)
12-<16 weeks	87 (2.7)	46 (1.5)	59 (1.9)	105 (1.7)
16-<24 weeks	123 (3.8)	77 (2.5)	84 (2.7)	161 (2.6)
24-<28 weeks	77 (2.4)	47 (1.5)	51 (1.7)	98 (1.6)
28-<50 weeks	238 (7.3)	175 (5.7)	162 (5.3)	337 (5.5)
≥50 weeks	2534 (77.7)	2581 (83.5)	2527 (81.9)	5108 (82.7)
≥76 weeks	1326 (40.6)	1435 (46.4)	1393 (45.2)	2828 (45.8)
Mean (SD)	64.37 (30.24)	68.77 (29.03)	67.44 (30.15)	68.11 (29.60)
Median	65.93	72.86	72.43	72.71
Range	(0.1;133.7)	(0.1;132.9)	(0.1;133.7)	(0.1;133.7)
Total Exposure (subject years)	4024.2	4075.5	3987.1	8062.6

Note: Total duration = Treatment duration = last dose date - first dose date + 1(in days).
Cross-reference: 4MSU Table 6, sub04r0401jul12rex.rtf generated by rex.sas, 17AUG2012 16:07

Attachment 10:
Baseline Demographic and Anthropometric Characteristics in Pooled Renal Impairment Dataset

	-- Placebo -- (N=382)	Cana 100 mg (N=338)	Cana 300 mg (N=365)	-- All Cana - (N=703)	--- Total --- (N=1085)
Sex, n (%)					
N	382	338	365	703	1085
Male	226 (59.2)	198 (58.6)	210 (57.5)	408 (58.0)	634 (58.4)
Female	156 (40.8)	140 (41.4)	155 (42.5)	295 (42.0)	451 (41.6)
Age (Years)					
N	382	338	365	703	1085
Category, n (%)					
<35	0	0	0	0	0
35 -<65	153 (40.1)	122 (36.1)	140 (38.4)	262 (37.3)	415 (38.2)
65 -<75	163 (42.7)	151 (44.7)	169 (46.3)	320 (45.5)	483 (44.5)
≥75	66 (17.3)	65 (19.2)	56 (15.3)	121 (17.2)	187 (17.2)
≥85	3 (0.8)	1 (0.3)	5 (1.4)	6 (0.9)	9 (0.8)
Mean (SD)	66.9 (7.57)	67.3 (8.10)	66.9 (7.39)	67.1 (7.74)	67.1 (7.67)
Median	67.0	68.0	67.0	67.0	67.0
Range	(45;96)	(35;85)	(40;90)	(35;90)	(35;96)
Race, n (%)					
N	382	338	365	703	1085
White	309 (80.9)	260 (76.9)	280 (76.7)	540 (76.8)	849 (78.2)
Black or African American	9 (2.4)	9 (2.7)	13 (3.6)	22 (3.1)	31 (2.9)
Asian	50 (13.1)	43 (12.7)	48 (13.2)	91 (12.9)	141 (13.0)
American Indian or Alaska Native	0	2 (0.6)	1 (0.3)	3 (0.4)	3 (0.3)
Native Hawaiian or Other Pacific Islander	2 (0.5)	2 (0.6)	2 (0.5)	4 (0.6)	6 (0.6)
Multiple	2 (0.5)	0	2 (0.5)	2 (0.3)	4 (0.4)
Other	9 (2.4)	21 (6.2)	19 (5.2)	40 (5.7)	49 (4.5)
Unknown	1 (0.3)	1 (0.3)	0	1 (0.1)	2 (0.2)
Ethnicity, n (%)					
N	382	338	365	703	1085
Hispanic or Latino	34 (8.9)	34 (10.1)	35 (9.6)	69 (9.8)	103 (9.5)
Not Hispanic or Latino	344 (90.1)	301 (89.1)	327 (89.6)	628 (89.3)	972 (89.6)
Not Reported	4 (1.0)	0	0	0	4 (0.4)
Unknown	0	3 (0.9)	3 (0.8)	6 (0.9)	6 (0.6)
Baseline BMI (kg/m²)					
N	381	337	363	700	1081
Category, n (%)					
<30	122 (31.9)	126 (37.3)	141 (38.6)	267 (38.0)	389 (35.9)
≥30	259 (67.8)	211 (62.4)	222 (60.8)	433 (61.6)	692 (63.8)
Mean (SD)	33.0 (6.20)	32.2 (6.10)	32.3 (6.05)	32.3 (6.07)	32.5 (6.12)
Median	32.3	31.6	31.9	31.8	32.1
Range	(18;56)	(19;57)	(19;55)	(19;57)	(18;57)
Region, n (%)					
N	382	338	365	703	1085
North America	135 (35.3)	130 (38.5)	136 (37.3)	266 (37.8)	401 (37.0)
Central/South America	16 (4.2)	13 (3.8)	14 (3.8)	27 (3.8)	43 (4.0)
Europe	100 (26.2)	105 (31.1)	102 (27.9)	207 (29.4)	307 (28.3)
Rest of the World	131 (34.3)	90 (26.6)	113 (31.0)	203 (28.9)	334 (30.8)

Note: Percentages calculated with the number of subjects in each group as denominator.
tsub02_02_rsl.rtf generated by rsl.sas, 18APR2012 16:15

Attachment 11:
Duration of Exposure to Study Drug in Pooled Renal Impairment Dataset

	----- Placebo ----- (N=382)	--- Cana 100 mg --- (N=338)	--- Cana 300 mg --- (N=365)	----- All Cana ---- (N=703)
Total duration of exposure (weeks)				
N	382	338	365	703
Category, n (%)				
<2 weeks	4 (1.0)	5 (1.5)	1 (0.3)	6 (0.9)
2-<6 weeks	13 (3.4)	4 (1.2)	12 (3.3)	16 (2.3)
6-<12 weeks	9 (2.4)	11 (3.3)	14 (3.8)	25 (3.6)
12-<16 weeks	12 (3.1)	5 (1.5)	7 (1.9)	12 (1.7)
16-<24 weeks	14 (3.7)	14 (4.1)	13 (3.6)	27 (3.8)
24-<28 weeks	116 (30.4)	112 (33.1)	109 (29.9)	221 (31.4)
28-<50 weeks	139 (36.4)	109 (32.2)	122 (33.4)	231 (32.9)
≥50 weeks	75 (19.6)	78 (23.1)	87 (23.8)	165 (23.5)
≥76 weeks	12 (3.1)	13 (3.8)	8 (2.2)	21 (3.0)
Mean (SD)	35.57 (17.61)	37.41 (18.44)	37.31 (18.34)	37.36 (18.38)
Median	30.57	30.79	32.14	31.43
Range	(0.1;89.4)	(0.1;90.4)	(1.3;91.4)	(0.1;91.4)
Total Exposure (subject years)	260.4	242.3	261.0	503.3

Note: Total duration = Treatment duration = last dose date - first dose date + 1(in days).
Cross-reference: 4MSU Table 23, tsub04r_02_rex.rtf generated by rex.sas, 18APR2012 16:49

Attachment 12:
Reasons for Withdrawal in Broad Dataset (through 01 July 2012)

Subject Disposition Category	All Non-CANA (N=3262) n (%)	CANA 100 mg (N=3092) n (%)	CANA 300 mg (N=3085) n (%)	All CANA (N=6177) n (%)	Total (N=9439) n (%)
Subjects who discontinued prior to the cutoff date	925 (28.4)	686 (22.2)	695 (22.5)	1381 (22.4)	2306 (24.4)
Primary reason for discontinuation	925 (28.4)	686 (22.2)	695 (22.5)	1381 (22.4)	2306 (24.4)
Adverse event	156 (4.8)	170 (5.5)	217 (7.0)	387 (6.3)	543 (5.8)
Creatinine or eGFR withdrawal criteria[a]	17 (0.5)	23 (0.7)	22 (0.7)	45 (0.7)	62 (0.7)
Death	30 (0.9)	21 (0.7)	17 (0.6)	38 (0.6)	68 (0.7)
Lack of efficacy on rescue therapy	33 (1.0)	8 (0.3)	6 (0.2)	14 (0.2)	47 (0.5)
Lost to follow-up	59 (1.8)	47 (1.5)	47 (1.5)	94 (1.5)	153 (1.6)
Noncompliance with study drug	21 (0.6)	19 (0.6)	9 (0.3)	28 (0.5)	49 (0.5)
Physician decision	39 (1.2)	30 (1.0)	22 (0.7)	52 (0.8)	91 (1.0)
Pregnancy	1 (<0.1)	1 (<0.1)	0	1 (<0.1)	2 (<0.1)
Protocol violation	22 (0.7)	24 (0.8)	14 (0.5)	38 (0.6)	60 (0.6)
Study terminated by sponsor	1 (<0.1)	1 (<0.1)	3 (0.1)	4 (0.1)	5 (0.1)
Withdrawal of consent[b]	145 (4.4)	90 (2.9)	102 (3.3)	192 (3.1)	337 (3.6)
Product quality complaint	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Unable to take protocol defined rescue therapy	38 (1.2)	17 (0.5)	15 (0.5)	32 (0.5)	70 (0.7)
Subject decided to discontinue early but agrees to be contacted (DIA3008)[c]	135 (4.1)	84 (2.7)	65 (2.1)	149 (2.4)	284 (3.0)
Other[d]	228 (7.0)	150 (4.9)	156 (5.1)	306 (5.0)	534 (5.7)

[a] eGFR <50 mL/min/1.73 m^2 or based upon local label contraindications for metformin use.
[b] Withdrawal of consent' also includes category of 'Subject withdrew consent for treatment and refuses any further follow-up' labeled separately in DIA3008.
[c] Category of 'Subject decided to discontinue early but agrees to be contacted' was labeled separately in DIA3008. In all other studies discontinuations due to this category are included in the category of 'other'.
[d] Other' includes categories labeled as 'Other, including other study-specific discontinuation criteria' in DIA3005, DIA3008 and DIA3009, 'Other, including other study-specific withdrawal criteria' in DIA3002, DIA3006, DIA3010 and DIA3012, 'Other, including study-specific discontinuation criteria not listed above' in DIA3004.
Note: Percentages calculated with the number of subjects in each group as denominator.
Cross-reference: 4MSU Table ; 4 tsub01b0401jul12rds04wd.rtf generated by rds04wd.sas, 07SEP2012 12:04

Attachment 13:
Adverse Events in At Least 2% of Subjects in Any Treatment Group by Body System and Preferred Term in Placebo-controlled Studies Dataset

Body System Or Organ Class Dictionary-Derived Term	Placebo (N=646) n (%)	Cana 100 mg (N=833) n (%)	Cana 300 mg (N=834) n (%)	All Cana (N=1667) n (%)
Total no. subjects with the AEs	371 (57.4)	500 (60.0)	494 (59.2)	994 (59.6)
Gastrointestinal Disorders	88 (13.6)	124 (14.9)	128 (15.3)	252 (15.1)
Constipation	6 (0.9)	15 (1.8)	19 (2.3)	34 (2.0)
Diarrhoea	28 (4.3)	26 (3.1)	37 (4.4)	63 (3.8)
Nausea	9 (1.4)	18 (2.2)	18 (2.2)	36 (2.2)
Infections and Infestations	180 (27.9)	247 (29.7)	241 (28.9)	488 (29.3)
Influenza	20 (3.1)	19 (2.3)	16 (1.9)	35 (2.1)
Nasopharyngitis	30 (4.6)	37 (4.4)	44 (5.3)	81 (4.9)
Sinusitis	11 (1.7)	17 (2.0)	8 (1.0)	25 (1.5)
Upper Respiratory Tract Infection	31 (4.8)	38 (4.6)	38 (4.6)	76 (4.6)
Urinary Tract Infection	23 (3.6)	45 (5.4)	33 (4.0)	78 (4.7)
Vulvovaginal Mycotic Infection	4 (0.6)	25 (3.0)	23 (2.8)	48 (2.9)
Metabolism and Nutrition Disorders	41 (6.3)	51 (6.1)	41 (4.9)	92 (5.5)
Hyperglycaemia	16 (2.5)	6 (0.7)	1 (0.1)	7 (0.4)
Hypoglycaemia	13 (2.0)	21 (2.5)	19 (2.3)	40 (2.4)
Musculoskeletal and Connective Tissue Disorders	83 (12.8)	93 (11.2)	104 (12.5)	197 (11.8)
Arthralgia	23 (3.6)	23 (2.8)	19 (2.3)	42 (2.5)
Back Pain	16 (2.5)	23 (2.8)	34 (4.1)	57 (3.4)
Nervous System Disorders	47 (7.3)	74 (8.9)	65 (7.8)	139 (8.3)
Headache	27 (4.2)	34 (4.1)	29 (3.5)	63 (3.8)
Renal and Urinary Disorders	13 (2.0)	61 (7.3)	52 (6.2)	113 (6.8)
Pollakiuria	4 (0.6)	35 (4.2)	26 (3.1)	61 (3.7)
Respiratory, Thoracic and Mediastinal Disorders	41 (6.3)	42 (5.0)	42 (5.0)	84 (5.0)
Cough	15 (2.3)	12 (1.4)	13 (1.6)	25 (1.5)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events, prior to use of rescue medication.

Cross-reference: Output TAE03R_01; tae03_01_rae2.rtf generated by rae2.sas, 18APR2012 16:13

Attachment 14:
Adverse Events in At Least 2% of Subjects in Any Treatment Group by Body System and Preferred Term in Pooled Renal Impairment Dataset

Body System Or Organ Class Dictionary-Derived Term	Placebo (N=382) n (%)	Cana 100 mg (N=338) n (%)	Cana 300 mg (N=365) n (%)	All Cana (N=703) n (%)
Total no. subjects with the AEs	269 (70.4)	250 (74.0)	275 (75.3)	525 (74.7)
Blood and Lymphatic System Disorders	15 (3.9)	6 (1.8)	4 (1.1)	10 (1.4)
Anaemia	12 (3.1)	2 (0.6)	3 (0.8)	5 (0.7)
Gastrointestinal Disorders	63 (16.5)	65 (19.2)	71 (19.5)	136 (19.3)
Constipation	7 (1.8)	8 (2.4)	10 (2.7)	18 (2.6)
Diarrhoea	21 (5.5)	9 (2.7)	24 (6.6)	33 (4.7)
Nausea	12 (3.1)	10 (3.0)	10 (2.7)	20 (2.8)
General Disorders and Administration Site Conditions	51 (13.4)	43 (12.7)	38 (10.4)	81 (11.5)
Chest Pain	7 (1.8)	5 (1.5)	9 (2.5)	14 (2.0)
Fatigue	8 (2.1)	9 (2.7)	8 (2.2)	17 (2.4)
Oedema Peripheral	16 (4.2)	8 (2.4)	8 (2.2)	16 (2.3)
Infections and Infestations	141 (36.9)	118 (34.9)	118 (32.3)	236 (33.6)
Bronchitis	15 (3.9)	10 (3.0)	9 (2.5)	19 (2.7)
Gastroenteritis	5 (1.3)	7 (2.1)	2 (0.5)	9 (1.3)
Influenza	10 (2.6)	10 (3.0)	7 (1.9)	17 (2.4)
Localised Infection	8 (2.1)	1 (0.3)	3 (0.8)	4 (0.6)
Nasopharyngitis	26 (6.8)	19 (5.6)	22 (6.0)	41 (5.8)
Pneumonia	9 (2.4)	5 (1.5)	4 (1.1)	9 (1.3)
Sinusitis	9 (2.4)	7 (2.1)	7 (1.9)	14 (2.0)
Upper Respiratory Tract Infection	25 (6.5)	21 (6.2)	20 (5.5)	41 (5.8)
Urinary Tract Infection	21 (5.5)	16 (4.7)	21 (5.8)	37 (5.3)
Injury, Poisoning and Procedural Complications	41 (10.7)	31 (9.2)	36 (9.9)	67 (9.5)
Contusion	9 (2.4)	2 (0.6)	6 (1.6)	8 (1.1)
Investigations	37 (9.7)	39 (11.5)	49 (13.4)	88 (12.5)
Blood Creatinine Increased	7 (1.8)	17 (5.0)	20 (5.5)	37 (5.3)
Blood Urea Increased	6 (1.6)	7 (2.1)	12 (3.3)	19 (2.7)
Metabolism and Nutrition Disorders	70 (18.3)	67 (19.8)	76 (20.8)	143 (20.3)
Hyperglycaemia	16 (4.2)	6 (1.8)	6 (1.6)	12 (1.7)
Hyperkalaemia	6 (1.6)	5 (1.5)	8 (2.2)	13 (1.8)
Hypoglycaemia	27 (7.1)	42 (12.4)	43 (11.8)	85 (12.1)
Musculoskeletal and Connective Tissue Disorders	68 (17.8)	53 (15.7)	59 (16.2)	112 (15.9)
Arthralgia	15 (3.9)	7 (2.1)	11 (3.0)	18 (2.6)
Back Pain	12 (3.1)	11 (3.3)	13 (3.6)	24 (3.4)
Muscle Spasms	9 (2.4)	3 (0.9)	9 (2.5)	12 (1.7)
Osteoarthritis	6 (1.6)	7 (2.1)	4 (1.1)	11 (1.6)
Pain in Extremity	6 (1.6)	11 (3.3)	8 (2.2)	19 (2.7)

Body System Or Organ Class Dictionary-Derived Term	Placebo (N=382) n (%)	Cana 100 mg (N=338) n (%)	Cana 300 mg (N=365) n (%)	All Cana (N=703) n (%)
Nervous System Disorders	45 (11.8)	52 (15.4)	43 (11.8)	95 (13.5)
Dizziness	3 (0.8)	6 (1.8)	8 (2.2)	14 (2.0)
Dizziness Postural	2 (0.5)	7 (2.1)	7 (1.9)	14 (2.0)
Headache	10 (2.6)	16 (4.7)	9 (2.5)	25 (3.6)
Renal and Urinary Disorders	37 (9.7)	37 (10.9)	41 (11.2)	78 (11.1)
Pollakiuria	7 (1.8)	7 (2.1)	9 (2.5)	16 (2.3)
Renal Impairment	6 (1.6)	8 (2.4)	9 (2.5)	17 (2.4)
Reproductive System and Breast Disorders	5 (1.3)	16 (4.7)	22 (6.0)	38 (5.4)
Balanitis	3 (0.8)	2 (0.6)	8 (2.2)	10 (1.4)
Respiratory, Thoracic and Mediastinal Disorders	37 (9.7)	33 (9.8)	24 (6.6)	57 (8.1)
Cough	10 (2.6)	10 (3.0)	7 (1.9)	17 (2.4)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events, regardless of rescue medication.
Cross-reference: Output TAE02brsae_02; tae03_02_rae2.rtf generated by rae2.sas, 18APR2012 17:19

Attachment 15:
Search Terms for Adverse Events of Neoplasms

Search terms for thyroid structural adverse events:

- Benign neoplasm of thyroid gland
- Haemorrhagic thyroid cyst
- Goitre
- Thyroid adenoma
- Thyroid cancer
- Thyroid cancer recurrent
- Thyroid cyst
- Thyroid neoplasm

Search terms for skin neoplasms:

- Basal cell carcinoma
- Dysplastic naevus
- Malignant melanoma
- Malignant melanoma in situ
- Melanocytic naevus
- Metastatic malignant melanoma
- Neoplasm skin
- Neuroendocrine carcinoma of the skin
- Seborrhoeic keratosis
- Skin cancer
- Skin papilloma
- Squamous cell carcinoma

Search terms for intestinal neoplasms:

- Colon adenoma
- Colon cancer
- Colon cancer metastatic
- Colorectal cancer
- Gastric adenoma
- Gastric cancer
- Gastrointestinal tract adenoma
- Intestinal adenocarcinoma
- Oesophageal carcinoma
- Rectal cancer
- Rectosigmoid cancer

Attachment 16:
Adverse Events Leading to Treatment Discontinuation in At Least 0.2% of Subjects in Any Treatment Group in Placebo-controlled Studies Dataset

Body System Or Organ Class Dictionary-Derived Term	Placebo (N=646) n (%)	Cana 100 mg (N=833) n (%)	Cana 300 mg (N=834) n (%)	All Cana (N=1667) n (%)
Total no. subjects with the AEs	20 (3.1)	36 (4.3)	30 (3.6)	66 (4.0)
Gastrointestinal disorders	6 (0.9)	5 (0.6)	2 (0.2)	7 (0.4)
Abdominal discomfort	2 (0.3)	0	1 (0.1)	1 (0.1)
Diarrhoea	3 (0.5)	1 (0.1)	1 (0.1)	2 (0.1)
Nausea	1 (0.2)	2 (0.2)	0	2 (0.1)
Infections and infestations	2 (0.3)	7 (0.8)	5 (0.6)	12 (0.7)
Pneumonia	0	3 (0.4)	0	3 (0.2)
Vulvovaginal mycotic infection	0	3 (0.4)	0	3 (0.2)
Investigations	2 (0.3)	6 (0.7)	9 (1.1)	15 (0.9)
Blood creatinine increased	0	0	2 (0.2)	2 (0.1)
Blood potassium increased	1 (0.2)	0	2 (0.2)	2 (0.1)
Glomerular filtration rate decreased	1 (0.2)	2 (0.2)	5 (0.6)	7 (0.4)
Weight decreased	0	2 (0.2)	1 (0.1)	3 (0.2)
Renal and urinary disorders	0	4 (0.5)	2 (0.2)	6 (0.4)
Pollakiuria	0	1 (0.1)	2 (0.2)	3 (0.2)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events, regardless of rescue medication.
Cross-reference: Output DAE02_OTHAC_01; dae02othac01rae2ds1.rtf generated by rae2ds1.sas, 13SEP2012 11:46

Attachment 17:
Adverse Events Leading to Treatment Discontinuation in At Least 0.5% of Subjects in Any Group in Pooled Renal Impairment Dataset

Body System Or Organ Class Dictionary-Derived Term	Placebo (N=382) n (%)	Cana 100 mg (N=338) n (%)	Cana 300 mg (N=365) n (%)	All Cana (N=703) n (%)
Total no. subjects with the AEs	22 (5.8)	19 (5.6)	28 (7.7)	47 (6.7)
Gastrointestinal Disorders	2 (0.5)	2 (0.6)	2 (0.5)	4 (0.6)
Diarrhoea	2 (0.5)	0	1 (0.3)	1 (0.1)
Investigations	2 (0.5)	2 (0.6)	1 (0.3)	3 (0.4)
Blood Creatinine Increased	2 (0.5)	2 (0.6)	1 (0.3)	3 (0.4)
Metabolism and Nutrition Disorders	0	1 (0.3)	3 (0.8)	4 (0.6)
Hyperkalaemia	0	0	2 (0.5)	2 (0.3)
Nervous System Disorders	3 (0.8)	1 (0.3)	1 (0.3)	2 (0.3)
Transient Ischaemic Attack	2 (0.5)	0	0	0
Renal and Urinary Disorders	3 (0.8)	2 (0.6)	7 (1.9)	9 (1.3)
Renal Impairment	3 (0.8)	0	4 (1.1)	4 (0.6)
Skin and Subcutaneous Tissue Disorders	2 (0.5)	3 (0.9)	2 (0.5)	5 (0.7)
Urticaria	0	2 (0.6)	0	2 (0.3)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events, regardless of use of rescue medication.
Cross-reference: TAE05brds_02; tae05brds_02_rae2a.rtf generated by rae2a.sas, 16MAY2012 14:29

Attachment 18:
Serious Adverse Events in At Least 0.2% of Subjects in Any Treatment Group in Placebo-controlled Studies Dataset

Body System Or Organ Class Dictionary-Derived Term	Placebo (N=646) n (%)	Cana 100 mg (N=833) n (%)	Cana 300 mg (N=834) n (%)	All Cana (N=1667) n (%)
Total no. subjects with the AEs	22 (3.4)	28 (3.4)	22 (2.6)	50 (3.0)
Cardiac disorders	3 (0.5)	5 (0.6)	0	5 (0.3)
Acute coronary syndrome	2 (0.3)	0	0	0
Coronary artery disease	0	2 (0.2)	0	2 (0.1)
Infections and infestations	5 (0.8)	10 (1.2)	3 (0.4)	13 (0.8)
Pneumonia	0	3 (0.4)	0	3 (0.2)
Skin and subcutaneous tissue disorders	0	2 (0.2)	1 (0.1)	3 (0.2)
Urticaria	0	2 (0.2)	0	2 (0.1)
Vascular disorders	1 (0.2)	1 (0.1)	3 (0.4)	4 (0.2)
Deep vein thrombosis	0	0	2 (0.2)	2 (0.1)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events, regardless of rescue medication.
Cross-reference: Output Table DAE03_OTHAC_01; dae03othac01rae2ds1.rtf generated by rae2ds1.sas, 13SEP2012 11:46

Attachment 19:
Serious Adverse Events in At Least 0.5% of Subjects in Any Group in Pooled Renal Impairment Dataset

Body System Or Organ Class Dictionary-Derived Term	Placebo (N=382) n (%)	Cana 100 mg (N=338) n (%)	Cana 300 mg (N=365) n (%)	All Cana (N=703) n (%)
Total no. subjects with the AEs	75 (19.6)	45 (13.3)	54 (14.8)	99 (14.1)
Cardiac Disorders	11 (2.9)	5 (1.5)	10 (2.7)	15 (2.1)
Cardiac Arrest	0	1 (0.3)	2 (0.5)	3 (0.4)
Cardiac Failure	4 (1.0)	1 (0.3)	1 (0.3)	2 (0.3)
Cardiac Failure Congestive	1 (0.3)	0	4 (1.1)	4 (0.6)
Coronary Artery Disease	3 (0.8)	0	1 (0.3)	1 (0.1)
General Disorders and Administration Site Conditions	10 (2.6)	1 (0.3)	4 (1.1)	5 (0.7)
Chest Pain	3 (0.8)	0	0	0
Sudden Death	4 (1.0)	0	2 (0.5)	2 (0.3)
Infections and Infestations	18 (4.7)	10 (3.0)	8 (2.2)	18 (2.6)
Bronchitis	2 (0.5)	0	0	0
Lower Respiratory Tract Infection	2 (0.5)	0	1 (0.3)	1 (0.1)
Pneumonia	4 (1.0)	3 (0.9)	2 (0.5)	5 (0.7)
Sepsis	2 (0.5)	0	0	0
Urinary Tract Infection	2 (0.5)	1 (0.3)	0	1 (0.1)
Injury, Poisoning and Procedural Complications	8 (2.1)	3 (0.9)	5 (1.4)	8 (1.1)
Joint Dislocation	2 (0.5)	0	0	0
Metabolism and Nutrition Disorders	6 (1.6)	4 (1.2)	5 (1.4)	9 (1.3)
Dehydration	2 (0.5)	1 (0.3)	1 (0.3)	2 (0.3)
Diabetic Foot	0	1 (0.3)	2 (0.5)	3 (0.4)
Hyperkalaemia	0	1 (0.3)	2 (0.5)	3 (0.4)
Musculoskeletal and Connective Tissue Disorders	7 (1.8)	2 (0.6)	1 (0.3)	3 (0.4)
Arthritis	2 (0.5)	0	0	0
Osteoarthritis	2 (0.5)	0	1 (0.3)	1 (0.1)
Nervous System Disorders	7 (1.8)	2 (0.6)	5 (1.4)	7 (1.0)
Syncope	1 (0.3)	0	2 (0.5)	2 (0.3)
Transient Ischaemic Attack	5 (1.3)	1 (0.3)	2 (0.5)	3 (0.4)
Renal and Urinary Disorders	6 (1.6)	5 (1.5)	8 (2.2)	13 (1.8)
Renal Artery Stenosis	0	2 (0.6)	0	2 (0.3)
Renal Failure Acute	1 (0.3)	2 (0.6)	2 (0.5)	4 (0.6)
Renal Impairment	2 (0.5)	1 (0.3)	3 (0.8)	4 (0.6)
Respiratory, Thoracic and Mediastinal Disorders	8 (2.1)	4 (1.2)	2 (0.5)	6 (0.9)
Dyspnoea	1 (0.3)	2 (0.6)	0	2 (0.3)
Dyspnoea Exertional	2 (0.5)	0	0	0
Surgical and Medical Procedures	0	2 (0.6)	0	2 (0.3)
Haemorrhoid Operation	0	2 (0.6)	0	2 (0.3)
Vascular Disorders	5 (1.3)	4 (1.2)	8 (2.2)	12 (1.7)
Deep Vein Thrombosis	0	0	2 (0.5)	2 (0.3)
Hypotension	2 (0.5)	0	0	0
Peripheral Arterial Occlusive Disease	2 (0.5)	1 (0.3)	0	1 (0.1)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events, regardless of use of rescue medication.

Cross-reference: Output TAE02BRSAE_02**;** tae02brsae_02_rae2a.rtf generated by rae2a.sas, 18APR2012 17:16

Attachment 20:
Fracture Definitions

Fracture Definitions (Mackey 2007)
Fracture events were defined as follows by the Fracture Adjudication Committee (FAC):
High Trauma Fracture High trauma fractures include those fractures resulting from severe trauma such as motor vehicle crashes, being struck by a vehicle or other fast-moving projectile, or to falls from greater than standing height (for example, falls off a ladder, chair, porch, table, or other raised surface, not including stairs).
Low Trauma Fracture Low-trauma fractures include all fractures due to falls from standing height or less; falls on stairs, steps, or curbs; moderate trauma other than a fall (for example collisions with objects during normal activities); and minimal trauma other than a fall (for example turning over in bed).
Pathological Fracture Pathologic fractures include those fractures occurring in an area that is weakened by another disease process such as a tumor, metastatic cancer of the bone, infection, inherited bone disorders, etc.
Stress Fracture Stress fractures include those identifiable fractures caused by repetitive stress.
Other Fracture Fractures that occur in patients that are not attributable to the definitions above.

Attachment 21:
Risk-Engine Predicted Changes in CV Risk